CFTRI-MYSORE
187
Peptic ulcer

1879 ① peptic ulcer
② stomach (15) gastric diseases
③ digestion
④ ulcerative process
⑤ gastric secretions
duodenal "
pathogenesis
pathologic physiology
ulcer diagnosis
" treatment

PEPTIC ULCER

PEPTIC ULCER

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CFTRI-MYSORE
1879
Peptic ulcer.

PREFACE

It is important to take stock occasionally of what is known and is not known with certainty regarding any disease which constitutes a problem. This is particularly true of peptic ulcer which ranks among the 12 most costly diseases and regarding which much experimental work has been done in the last 30 years.

This book is an ambitious attempt to present systematically all the worthy information and thought which bears upon the problem of peptic ulcer. The general principles which the facts imply regarding the cause, diagnosis, and treatment of the disease are derived by making a critical analysis of the assembled and collated facts on each aspect of the problem. This is done with the idea of promoting sound thinking, teaching, and research on the subject and directing attention to the principles used in the treatment of peptic ulcer.

Dr. Bachrach, in reviewing the literature on experimental peptic ulcer for his Ph.D. thesis, in 1935 recognized the need for a comprehensive and critical survey of the subject. It is then that this book had its beginning. During the ensuing three years he and his wife, Gertrude, compiled a typewritten monograph on experimental peptic ulcer. In 1941 Dr. Grossman undertook to bring the work up to date and to put it into a form suitable for publication. After World War II it was decided, after many discussions with investigators and practicing physicians, to enlarge the scope of the work to include all of the important information from the clinical literature. With the assistance of Drs. Bachrach and Grossman and a number of graduate students, Dr. Ivy has put this material into a form which, we trust, will meet the needs of everyone interested in the subject.

We have attempted to achieve the aim of the book by the method of clinical science, which assembles, integrates, interprets, and applies the results of correlated studies on living men in health and disease, on dead men, and on lower animals.

Part I is titled "Introduction to the Problem of Peptic Ulcer" and considers basic topics, such as the resistance of the stomach, duodenum, and jejunum.

Part II brings extensive experimental, autopsy, and clinical observations to bear on the subject of the pathogenesis of peptic ulcer.

In this connection, it is frequently said that the etiology of peptic ulcer is unknown. However, when all the facts are assembled and evaluated, one finds that more is known than has been suspected and that the conditions required for the formation of a peptic ulcerative defect can be stated rather precisely.

This does not mean that the problem of the cause of peptic ulcer has been solved. It is a common error in medicine, based on the concept of the cause of specific infectious diseases, to set out to discover "the" cause of a disease. In the case of peptic ulcer, although we cannot state categorically that "the" cause is known, the most important factors essential for ulcer formation are known. Other factors are probably yet to be discovered and their relative importance evaluated.

Part III deals with the diagnostic problem, particularly of duodenal ulcer.

Part IV discusses medical and surgical therapy from the viewpoint of physiologic principles. It presents a summary of the clinical effectiveness of the various therapeutic procedures used today and points out the ideal therapeutic goal of tomorrow.

Each of the twenty-one chapters in the book is concluded with a summary and each of the parts is concluded with a summarizing chapter. This is to avoid telling so much that the reader is left uninformed and to prevent the reader from groping for scraps of useful information.

It is hoped that our efforts will serve as a guide to those who are or will become interested in contributing to the final or complete solution of the problem; if so, our efforts will be truly compensated.

Since one of the main purposes of the book is to present an accurate and reasonably complete consideration of the subject, we will be grateful to those who call our attention to omissions and significant inaccuracies, which must have occurred despite our efforts to avoid them.

Many persons have contributed to the completion of this volume. Assistance in reviewing and compiling literature was given by Dr. A. Littman on the subject of Medical Treatment and Dr. Henry Janowitz on the subject of Diagnosis. Dr. David Fainer spent a number of months compiling and analyzing the enormous literature on Surgical Treatment of Peptic Ulcer.

Our special thanks are due to Mr. Tom Jones and the members of his staff of the Illustration Studios, especially Mrs. Virginia Samter and Mrs. Ruth Best, for the preparation of the photographs and drawings.

The bibliographic references were checked for accuracy by Dr. David Fainer and Miss Elizabeth Faler. Mrs. Pauline Tureman of the Army Medical Library, Miss Janet Doe of the New York Academy of Sciences Library and Mr. Kenneth H. Fagerhough of the John Crerar Library

assisted in checking references. Miss Georgia Price of the Archibald Church Library at Northwestern University Medical School gave much library assistance in the earlier phases of the writing.

Able stenographic assistance, during the many drafts of this book, was given by Miss Virginia Reilly, Mrs. Gwen Lyman, Miss Mary Damgaard, Miss Doris Nielsen, and Miss Elizabeth Faler.

The Index of Authors (with approximately 5,000 entries) was compiled by the indefatigable Miss Elizabeth Faler.

To all of these, our sincere thanks.

THE AUTHORS.

FOREWORD

Sara M. Jordan, M.D.

Donald C. Balfour, M.D.

A. J. Carlson, Ph.D., M.D.

This momentous book may well be labelled the magnum opus of a man who has always been a stimulating example of undaunted courage and energy in attacking a problem, for in it the problem of peptic ulcer has been attacked, analyzed, and set before us in all its phases in an unprecedented form.

The simplicity of approach with its four parts, Definition, Pathogenesis, Diagnosis, and Treatment, gives little indication of the exhaustive review and analytical critique of what must be the complete literature on all phases of the ulcer problem. The extent of the literature analyzed is an indication of the complexity of this problem, and with the Outlines, Considerations, Comments and Summaries, as well as the summarizing chapters, the authors bring order out of the chaos of conflicting experimental and clinical data. In the numerous instances where the authors have made original contributions, their work is objectively evaluated and correlated with that of others. Of great interest to clinicians is the revelation of the multiplicity and interdependence of factors in the production of experimental ulcer and the superimposition of one factor upon another. The comment that it is pure sophistry to try to differentiate struck a sympathetic echo in my clinical experience. Only the author's wisdom, born of long experience, could engender such a skillful coördination of data from production of ulcer in the rabbit and dog with the pathogenesis of ulcer in man, as well as the differentiating deductions from the behavior of the acute and chronic ulcer. The exposition of the psychosomatic theory of etiology is of great interest at the moment, and very apt is the suggestion that the word "emotogenic" be substituted for "psychic," leaving the latter to the original connotation of Pavlov. The "number of mechanisms concerned in preserving the integrity of the mucosal cells" and the number of factors which violate that integrity are revealed in a manner which lends a dramatic quality to experimental medicine. And

perhaps the most valuable contribution of all is the constantly appearing suggestion, arising out of these critical analyses, that in this or that phase of the problem more work should be done to clarify it. The young and the eager should find many stimuli to further investigation toward the solution of the ulcer problem.

The two parts dealing with diagnosis and treatment are likewise cyclopedic. A complete history of all stages in the diagnosis of this disease is followed by an equally complete exposition of all forms of treatment. An objective and critical analysis of both these aspects of the disease and of medical and surgical therapy leads to the concluding sentences, dynamic in their simplicity: "Everyone, however, looks forward to the day when mutilating operations will be unnecessary. Present knowledge provides the basis for hope that future research will reveal an orally active, innocuous substance for specifically preventing the formation of acid by the parietal cell and for rendering the gastric and duodenal mucosa less susceptible to injury." It is the essence of understatement to say that Doctor Ivy's book, by its informative and stimulating effect, will be a great contribution toward that goal.

Sara M. Jordan
Lahey Clinic
Boston, Mass.

In the development of the surgical treatment of peptic ulcer through the years certain basic principles have become fairly well established. It is generally accepted today that uncomplicated duodenal ulcer is primarily a medical disease and gastric ulcer is primarily surgical, and that recurrent ulcer following surgical treatment usually requires further operation. In following such principles surgery has achieved much in the cure and control of peptic ulcer; the best results are attained by strict adherence to the intelligent selection of patients for operation, by the proper choice and conduct of the surgical procedure and by appropriate preoperative and postoperative management.

The accumulated experience of surgeons throughout the world has shown, however, that even when these requirements are fulfilled, some failures to control the tendency to have ulcer will occur, and surgeons have recognized this possibility in their approach to surgical treatment today. In some cases the reason for the disappointing result is obvious. In too many, however, no satisfactory explanation can be found, except the vague generalization that the factors responsible for the original ulcer

have not been sufficiently modified or eliminated to prevent recurrence. Since these factors are so intimately related to altered physiologic function in its broadest sense, it is obvious that further advances in the management of peptic ulcer, whether medical or surgical, will come from continued clinical and physiologic study of this relationship. In the vigorous pursuit of a solution to this problem by physiologists, clinicians and surgeons it is obvious that the present-day management of peptic ulcer rests upon the work of the experimental physiologist, which has established and verified fundamental concepts.

To our present knowledge of physiology of digestion in health and disease in general, and to our knowledge of peptic ulcer in particular, Andrew C. Ivy and his associates have contributed immeasurably. This volume on peptic ulcer should be enthusiastically welcomed since it brings together and interprets the significant contributions on the broad subject of gastric physiology and peptic ulcer in a manner such as only one with Dr. Ivy's experience and understanding could do. It is this, which makes the publication a milestone in the history of peptic ulcer.

The section on surgical therapy is an unprecedented assembling of data on every aspect of the basic principles upon which surgery of peptic ulcer is based, and it is in itself an important contribution to the surgical literature of the subject. This must have involved a prodigious amount of work through the years, and the surgical profession will appreciate Dr. Ivy's unusual ability to present and coördinate the experiences and opinions of others in all countries. The evaluation of such voluminous statistics is always difficult, but Dr. Ivy and his associates have succeeded in a remarkable way in drawing conclusions which are clear and well founded, and the surgeon will find the observations on the perplexing problems still inherent in the surgical therapy of peptic ulcer of great value. In discussing results, the authors clearly show why some surgical procedures have been ineffective and offer constructive suggestions for avoiding failures; this is what the surgeon wants to know. All in all, one is constantly aware, in reading the section on the surgical therapy of peptic ulcer, of a basic understanding of the disease and its complications from a physiologic, clinical and surgical standpoint.

The publication of this book is a significant event in medicine. I am sure that surgeons throughout the world will feel, as I do, that this volume on peptic ulcer splendidly reflects the great and inspiring influence which Dr. Ivy has had in the development and clarification of our knowledge of such an important and widespread disease.

Donald C. Balfour
Mayo Clinic
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The challenge of gastric and duodenal ulcer has in the last fifty years brought forth a very large volume of publications on the factors that may contribute to the production, the chronicity and the therapy of these maladies. Some of these published reports, clinical and experimental, do not measure up to scientific standards as regards controls and conclusions. And, despite the significant progress in the therapy of gastric and duodenal ulcers, we have not yet reached first base in their prevention.

The senior author of this volume has a wide experience in this field of biology and medicine. He has rendered a great service in producing this critical review of the most significant part of this large volume of literature. There are, clearly, not one but many factors, including involuntary nervous states, contributing to the initiation and chronicity of gastric and duodenal ulcers. The relative importance of some of these factors may vary from patient to patient.

The authors' critical summary of our knowledge of this field to date helps to change the classical question: "where do we go from here?" to the guide post: *where we should go from here*. This is a *must* book, not only for our colleagues in general practice but also for our colleagues in internal medicine, surgery, psychiatry and physiology.

A. J. Carlson
University of Chicago
Chicago, Ill.

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PART I

Introduction to the Problem of Peptic Ulcer

The chapters in this section of the book present information considered necessary for an approach to an understanding of the problem of peptic ulcer.

OUTLINE OF CHAPTER 1

Definition

I. Introduction

II. Definition of an Ulcer

A. general definition of an ulcer

B. definition of an ulcer as applied to the upper digestive tract

1. Anatomy
2. Definition of an Ulcer
3. Relation of Erosion and Ulcer
4. Other Terms

III. Acute and Chronic Ulcers of the Upper Digestive Tract

IV. Usage of the Term "Peptic Ulcer"

V. Summary

CHAPTER 1

Definition

> Though the lesion is called *the* ulcer, it is neither single nor definite in its nature and origin, and is often present in the plural number. Though it is called the *simple* ulcer, its characters are generally a compound of two processes of absorption and reaction, the latter of which certain instances show to be quite independent of the former. Though it is called the *chronic* ulcer, its progress is sometimes so rapid, as to penetrate the stomach and destroy life, in a few days. And, finally, though it is called the *perforating* ulcer, in about seven out of every eight cases it does not perforate.
>
> WILLIAM BRINTON (1865)[33]

Introduction

The purpose of this chapter is to clarify and define the terminology of ulcerative lesions of the upper digestive tract. We consider such clarification desirable because of the difficulty we have encountered in evaluating experimental observations, case reports, and autopsy protocols where the term "ulcer" is used indiscriminately and without uniformity.

Attention has been called to this point by various authors at intervals during the past century (1). To cite one example, Stierlin (2), in 1920, observed "numerous duodenal ulcers" in a dog with bilateral vagotomy and extirpation of the celiac plexus; when he examined these lesions microscopically, he recognized that they were not ulcers but were the result of either agonal or postmortem digestion of the mucosa, or of the surface epithelium overlying lymph follicles. He concluded rightly that observations on the experimental production of ulcers should be evaluated by a microscopic examination of the lesions, and that, in the study of the pathogenesis of acute lesions of the gastric and duodenal mucosa, the role played by terminal and postmortem digestion should be considered.

In spite of similar injunctions (3) published from time to time, even normal structures are still occasionally called chronic ulcers. For instance, figure 1 is a photograph similar to one which appeared in the literature as recently as 1938 with the caption "Specimen shows the isolated duodenum with 6 definite ulcers." Actually, it depicts the circumscribed depressions of the duodenal mucosa which occur normally in the dog at the site of lymph follicles or "Peyer's patches"; these structures are sometimes referred to colloquially as "freshman ulcers."



FIG. 1. Four lymph follicles or Peyer's patches in the duodenum just below the pylorus in the dog. These have been called ulcers by the inexperienced investigator.

Definition of an Ulcer

Since "ulcer" is a term applicable to the skin, cornea, and mucous membranes, we must establish first a general definition of the term.

Various authorities differ in their conceptions of what constitutes an ulcer. This lack of uniformity may be illustrated by quoting first some definitions from dictionaries. An ulcer is "an interruption of continuity of a surface, with an inflamed base" (4). An ulcer is "a lesion of a cutaneous or mucous surface, caused by molecular disintegration of the superficial parts, attended usually by more or less suppuration. A wound, due to traumatism, is not primarily an ulcer, but may become such if the healing process is arrested or the wound becomes infected with pyogenic organisms" (4a). An ulcer is "an open sore other than a wound; a loss of substance on a cutaneous or mucous surface, causing gradual disintegration and necrosis of tissues" (5). An ulcer is "a solution of continuity occurring upon the surface of the skin or any of the mucous membranes and causing gradual disintegration and necrosis of the tissues; a sore discharging pus. It is distinguished from an abscess, which has its beginning, at least, in the depth of the tissue" (6). An ulcer is "medically, a breach of either an external or internal surface, occurring in the course of a disease and accompanied by a loss of tissue" (7). An ulcer is "an erosive solution of continuity in any external or internal surface of the body, forming an open sore attended with secretion of pus or other morbid matter" (8).

Current American textbooks of pathology also lack uniformity in their definition of the term "ulcer." Boyd (9) says that "when an abscess reaches a surface, either skin or mucous membrane, the overlying tissue becomes necrosed, forming a slough, and when the slough is discharged an open sore or ulcer is produced. . . . An ulcer, which is an *open sore*, an interruption of surface continuity of skin or mucous membrane with accompanying inflammation, is, of course, frequently produced by injurious agents acting directly on the surface." Karsner (10) writes, "ulcer may be defined as an interruption of surface continuity with an inflammatory base." . . . "Ulcers may be found on any surface of the body and may be due to traumatic destruction of the surface, or result from degeneration, necrosis or inflammation in the neighborhood, which leads to the sloughing of the injured superficial tissue from the underlying parts." . . . "In more prolonged types of ulcer, the base is likely to show, in addition to serous exudation, considerable infiltration by the cells seen late in the course of inflammation." Smith and Gault (11) write, "By the term ulcer is meant a break in the continuity of any surface or lining epithelium, whether skin or mucous membrane, as the result of some necrotic inflammatory process. But ulceration implies more than mere superficial *abrasion* of the epi-

thelium which might easily result from mild trauma, such as falling and scraping the skin. It implies a lesion which has extended to, or begun in, the deeper structures of the skin or mucous membrane. Indeed, as a rule, in healing, a permanent cicatrix results from the replacement fibrosis which develops." According to Moore (12), "an abrasion is a superficial interruption in the continuity of the epidermis and dermis—in lay terms it is a scratch. There are loss of epithelium and slight hemorrhage into the dermis." He does not define "ulcer." Bell (13) says, "On mucous membranes or skin the sloughing off of necrotic tissue results in an ulcer."

Dermatologists, too, define ulcer variously, though all distinguish between an ulcer and an excoriation or abrasion. Ormsby and Montgomery (14) write that "ulcers are losses of substance resulting from pathological processes involving the corium. Excoriations (abrasions, erosions) are superficial solutions of continuity, usually involving portions of the skin, accompanied with itching and resulting from mechanical violence." Sutton and Sutton (15) write "ulcers are irregularly-sized and shaped excavations of the integument due to injury or disease." . . . "Because ulcers are losses of connective tissue structure, healing is accomplished by fibrotic proliferation and replacement, and this is scar." . . . "Excoriations are discontinuities of the skin, usually superficial in character and traumatic in origin." . . . "Epithelial discontinuities heal by replacement of epithelial cells. . . . No scar results." Andrews (16) defines ulcers as "destructive excavations," which may be "shallow," and, in the case of the skin, involving "only the epidermis," "or they may extend deep into the corium or even reach into the subcutaneous structures." "An excoriation (abrasion, erosion) is a superficial displacement of skin tissue, usually involving only the epidermis and rarely reaching the papillary layer of the corium," being due to trauma.

General Definition of an Ulcer

The foregoing definitions, in essence, characterize an ulcer as a loss of continuity of skin or mucous membrane due to trauma, necrosis, or inflammation; it is deeper than an abrasion, usually shows some degree of surrounding inflammation, and heals with the formation of scar tissue. A wound, such as a cut, stab puncture or rent, though not an ulcer, is sometimes so designated if healing is delayed. Excoriations, abrasions, or erosions may develop into ulcers if they become infected and then extend through all layers of the skin; but these terms are used only to refer to the primary surface lesion.

An analysis of the characteristics just presented reveals that the essential feature of an ulcer, as distinguished from more superficial lesions

(erosions and abrasions), is its failure to heal solely by regeneration of the lost elements with complete restitution of original structure. The basic condition necessary for the formation of granulation tissue and subsequent scarring is that the lesion must extend to tissue of a type over which epithelium cannot regenerate. At the site of removal of a split-thickness skin transplant, the papillae of the dermis are covered rapidly by the adjacent epithelium; similarly, when gastric glands or intestinal villi are transected, the connective tissue stroma is involved but the epithelium regenerates directly over it. This is because the epithelial tissues of the body normally lie upon a type of connective tissue over which the epithelial cells can migrate and take hold. When the defect in an epithelial surface extends deeply enough to involve a different type of tissue, a type over which epithelial cells cannot migrate, then a process of replacement proliferation takes place, the purpose of which is to provide a connective tissue stratum similar to that upon which epithelium normally rests.

The destruction of the epithelial layer must be *complete* within a circumscribed area if granulation and scarring are to be a factor in the repair process. Therefore, *an ulcer may be defined as a circumscribed complete loss of epithelial elements with proliferation of connective tissue.*

This definition is based on the anatomic characteristics of the lesion, and it is in essential agreement with the definitions given by pathologists, particularly Karsner (10).

Definition of an Ulcer as Applied to the Upper Digestive Tract

Anatomy

It is necessary to keep in mind the anatomy of the wall of the stomach, duodenum, and jejunum in order to consider the application of the general definition of an ulcer to lesions of these organs.

The *wall of the stomach* is composed of several layers (Fig. 2). The mucosa of the stomach consists of two layers, the surface epithelium and the glandular layer. The glandular layer contains the gastric glands which are surrounded by connective tissue, blood vessels, lymphatic vessels, and nerves. The muscularis mucosae lies external to the layer of glands.

The *wall of the duodenum* has the same layers as the stomach, but in the case of the duodenum the glands of Brunner (glandulae duodenales) are located for the most part in the submucosa (Fig. 3).

The *wall of the jejunum* is much like the duodenum (Fig. 4). Though not generally recognized, the upper jejunum of man contains groups of Brunner's glands (17). This is not true of the dog and of most laboratory animals.

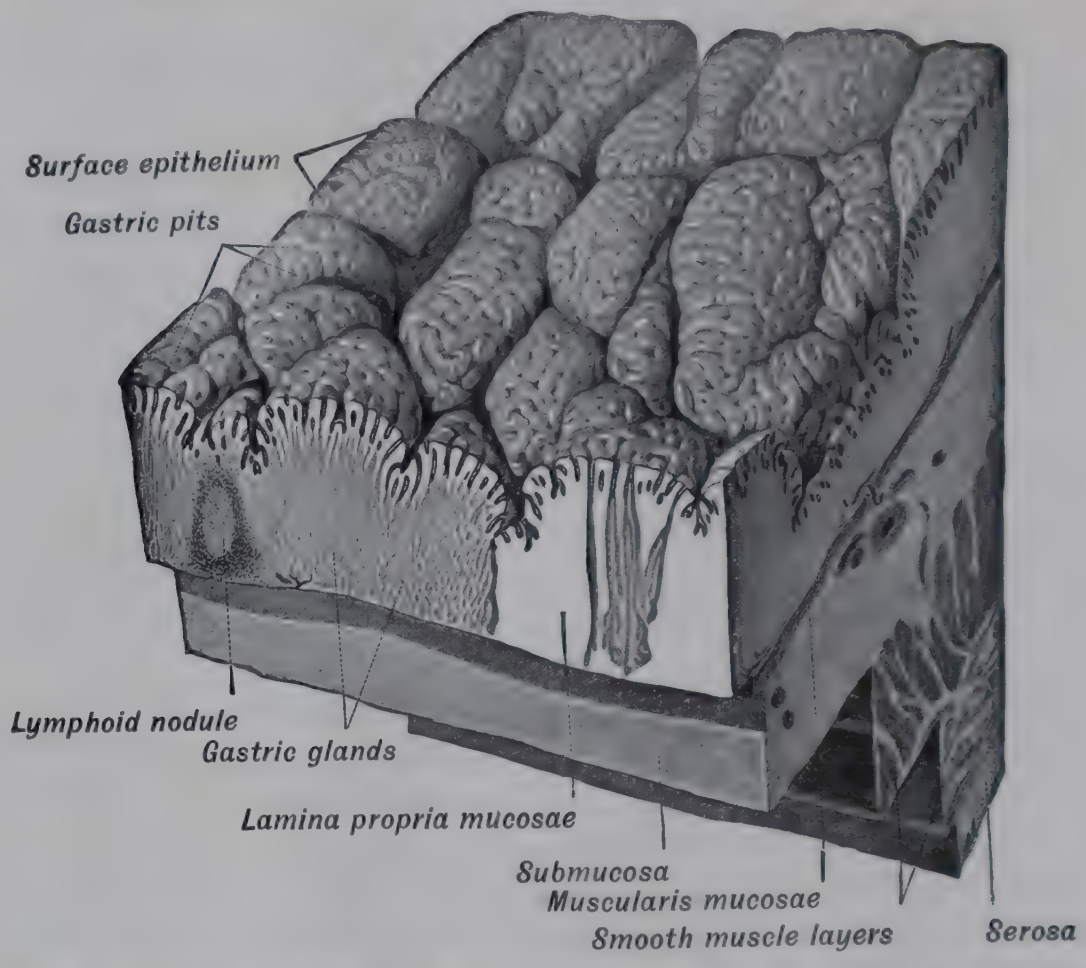


FIG. 2. Surface of the gastric mucosa of an executed man. Drawn with a binocular microscope. The cut surfaces are slightly diagrammatic. (Courtesy, Maximow and Bloom: "Textbook of Histology," W. B. Saunders Co.)

Definition of an Ulcer

A circumscribed defect in the mucosa of the stomach, duodenum, and jejunum is called an ulcer only when the defect extends through the muscularis mucosae. Only then is the continuity of the mucosa lost *completely*, and on healing does a scar result.

In speaking of circumscribed defects extending from the lumen of the viscera, two terms in common usage are erosion and ulcer; regarding these terms, Stewart (19) observed that "there appear to be no valid grounds for drawing a distinction, except possibly the depth of the lesion. . . ." It is our contention that (a) the depth provides a definite basis for differentiating the two lesions, and (b) an anatomic distinction is desirable as long as there is any doubt concerning their etiologic relationship. On this second point we see no reason for departing from the teachings of Rokitansky (24), who wrote: " . . . erosion doubtless occurs sometimes as an idiopathic disease . . . but more often it is seen . . . in association with the various acute and chronic illnesses, so that the intimate nature of the process . . . is open to question. Its recognition is nevertheless important

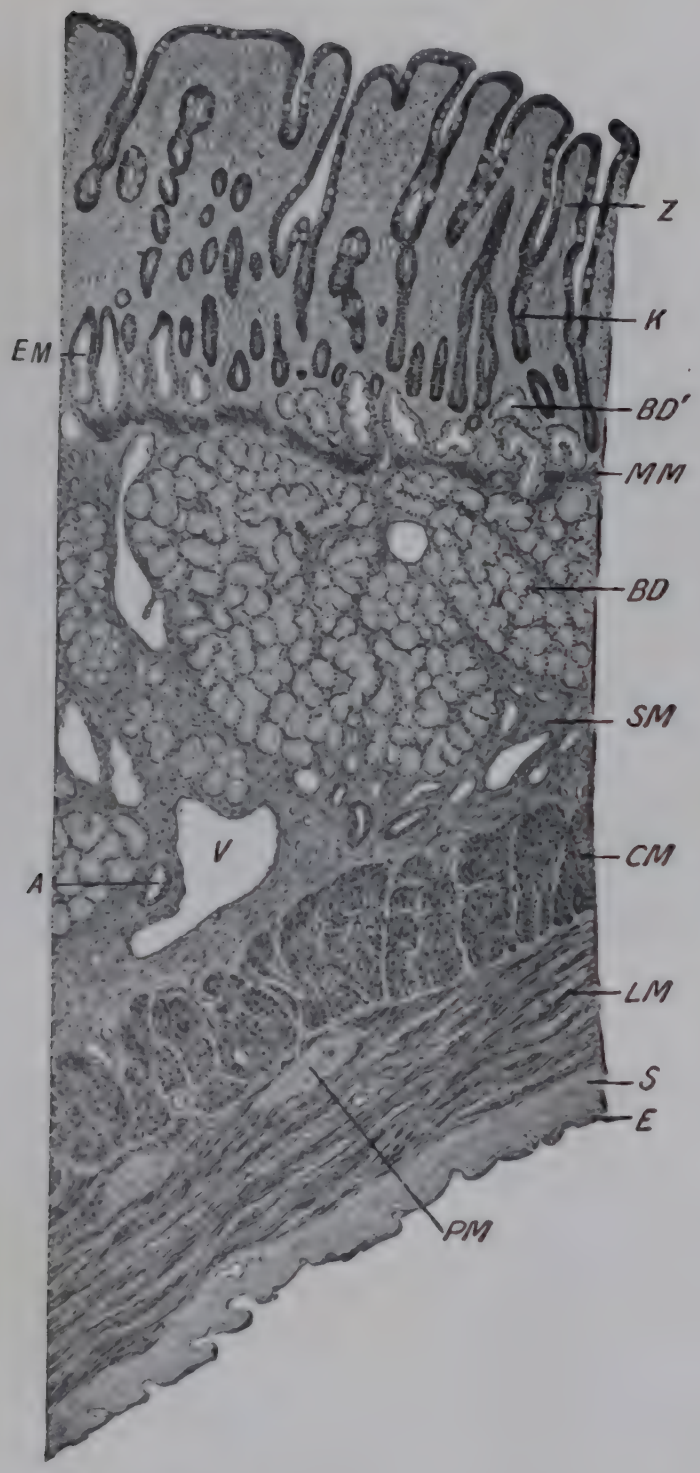


FIG. 3. From a longitudinal section through the duodenum of man: *A*, artery; *BD*, Brunner's glands in the submucosa; *BD'*, Brunner's glands in the mucosa; *CM*, circular muscle cut across; *E*, mesothelium of serosa; *EM*, emptying of a Brunner gland into a crypt; *K*, crypt of Lieberkühn; *LM*, longitudinal muscle layer; *MM*, muscularis mucosae; *PM*, plexus myentericus with a ganglion cell in cross section; *S*, serosa; *SM*, submucosa; *Z*, villus. 30 ×. After Schaffer. (Courtesy, Maximow and Bloom: "Textbook of Histology," W. B. Saunders Co.)

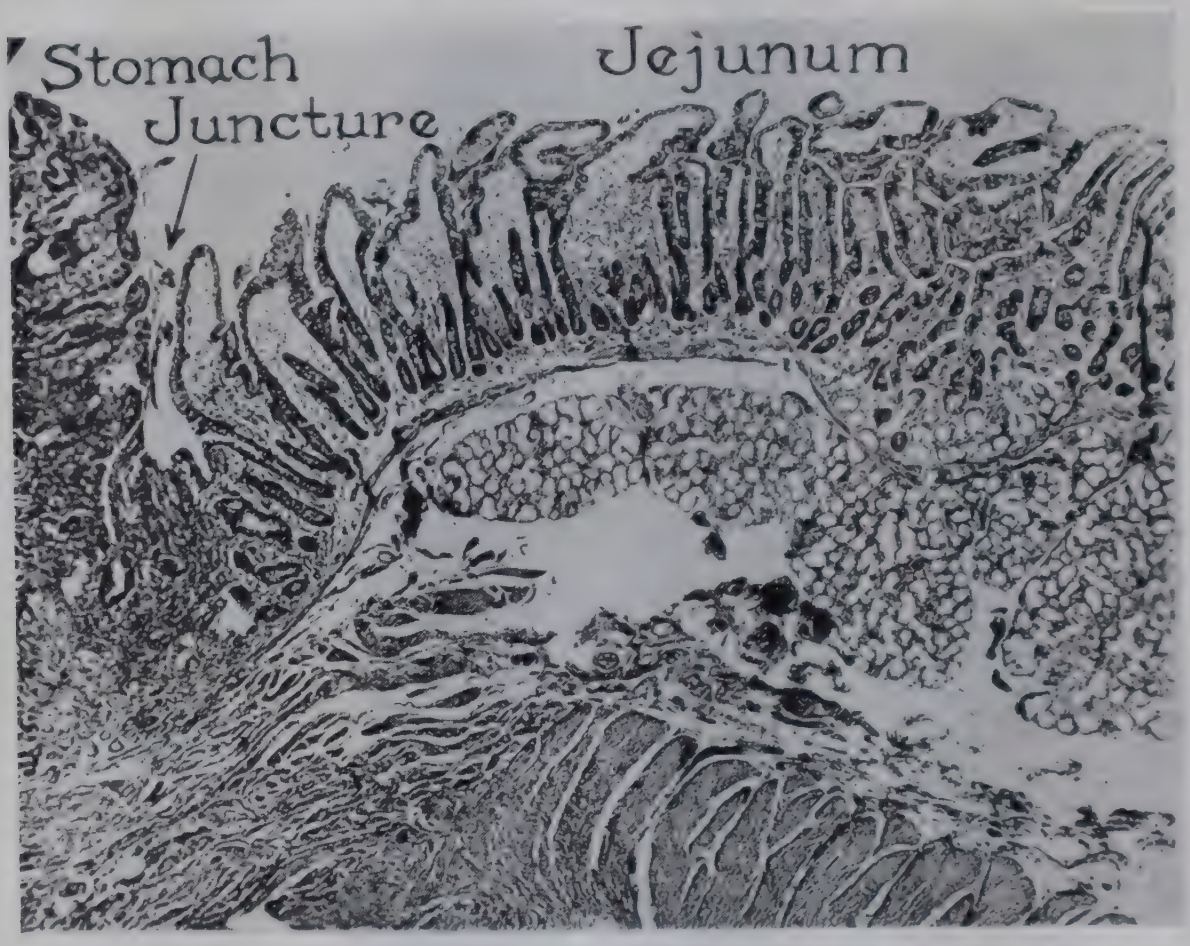


FIG. 4. Gastrojejunal stoma 22 years old. Note Brunner's glands on the jejunal side of the anastomosis between the muscularis mucosae and the muscular layer. (Courtesy, Rosenow and McDonald: *Gastroenterology*, **2:** 165.)

if only in the limited sense that one knows that it is a spontaneous process and has nothing in common with erosion by corrosive substances." Or, as Hauser (32) puts it: "Even if it be theoretically correct that erosion and ulcer are not to be separated as to pathogenesis, . . . they nevertheless differ in their basically dissimilar course of healing, in their clinical significance, and indeed in many cases also etiologically in certain respects, so that a distinction between the two in a fundamental sense appears decidedly justified."

Relation of Erosion and Ulcer

An erosion is a defect which does not penetrate the entire thickness of a mucous membrane (Figs. 5 and 6). In those mucosae which have a muscularis mucosae, an erosion is a defect which does not penetrate the muscularis mucosae.

An ulcer is a defect which penetrates the entire thickness of a mucous membrane. In the case of the stomach, duodenum, and jejunum, an ulcer is a defect which penetrates the muscularis mucosae and frequently into and occasionally through the remaining layers. Contrary to Aschoff (1), the diameter of the lesion provides no adequate basis for differentiation.

Thus, by definition, the only distinction between an erosion and an ulcer is depth; this concept is in accord with Bockus (21) and is in essential agreement with Hauser (32), who bases the distinction on the fundamentally different kinds of healing of the two forms. The defect of the mucous membrane alone, the erosion, heals by epithelial regeneration without scar formation; the defect which extends through the muscularis mucosae heals by means of granulation tissue formation.

Other Terms

The expression "*superficial ulcer*," or "*superficial acute ulcer*," is sometimes used to refer to an erosion as defined above, or to an ulcer which penetrates either to the muscularis mucosae or to the submucosa. Stewart (19) was of the opinion that "if the term erosion is to be retained at all, it ought to be used merely as a synonym for a very superficial acute ulcer. . . . " But such terms as "superficial" and "very superficial" are subjective expressions, and we do not favor their use as a basis for distinguishing ulcerative lesions.

In describing the *appearance* or *genesis* of an ulcer, there are a number of useful terms such as penetrating, spreading, perforating, calloused, indurated, saddle, round, irregular, punched-out, funnel-shaped, serpigi-

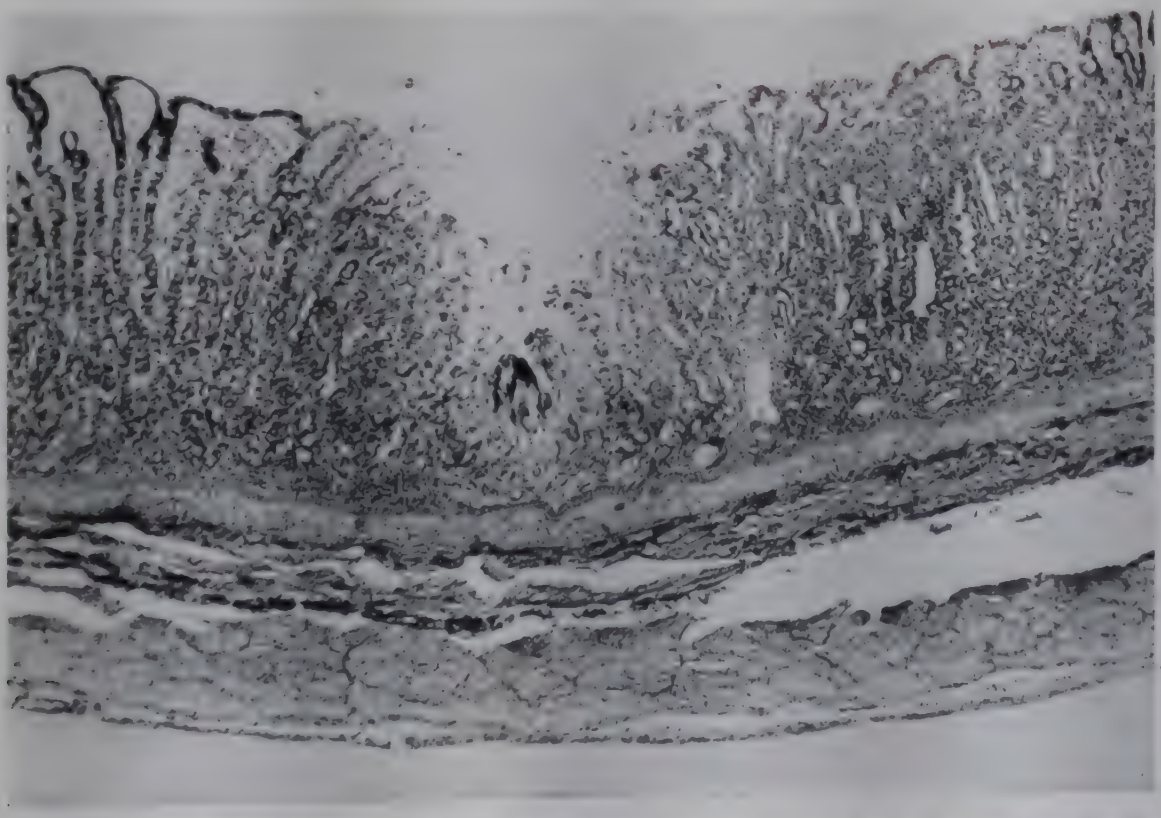


FIG. 5. A small erosion of the gastric mucosa. Note that the defect in the mucosa does not completely extend to the muscularis mucosae. Also note the thrombosed vein.

nous, cleft-like, terraced, follicular, hemorrhagic, tuberculous, syphilitic, carcinomatous, peptic, traumatic, embolic, and others (18–21).

A term which enjoys considerable usage in relation to peptic ulcer is the word "active." Clinically, an "active ulcer" apparently connotes a peptic ulcer during a recurrence, or when it is causing symptoms. So, the "activity" of an ulcer is a function not of its anatomic characteristics so much as of its clinical manifestations. However, even this conception is not clear cut, because occasionally the gastroscopist or radiologist will describe an ulcer as "still active," meaning that it is not healed in a follow-up examination even though the symptoms have abated. In this sense, the term is used to describe an unhealed ulcer. On the other hand, when an ulcer is designated "inactive," it implies a symptom-free period in an ulcer patient; the lesion may be present but not productive of symptoms, or it may be healed. This is distinctly different from a "silent" ulcer, which is an incidental lesion, not known to have given rise to any complaints on the part of the individual harboring it until it suddenly bleeds or perforates or is discovered at autopsy.

Hurst and Stewart (19) characterize an ulcer as "active" on anatomic grounds when there is infiltration of polymorphonuclear neutrophils, as contrasted with the callous nonreacting chronic ulcer which is characterized by fibrosis and by infiltration with lymphocytes and eosinophils. If an ulcer of the latter description shows a focus of neutrophils, it is said

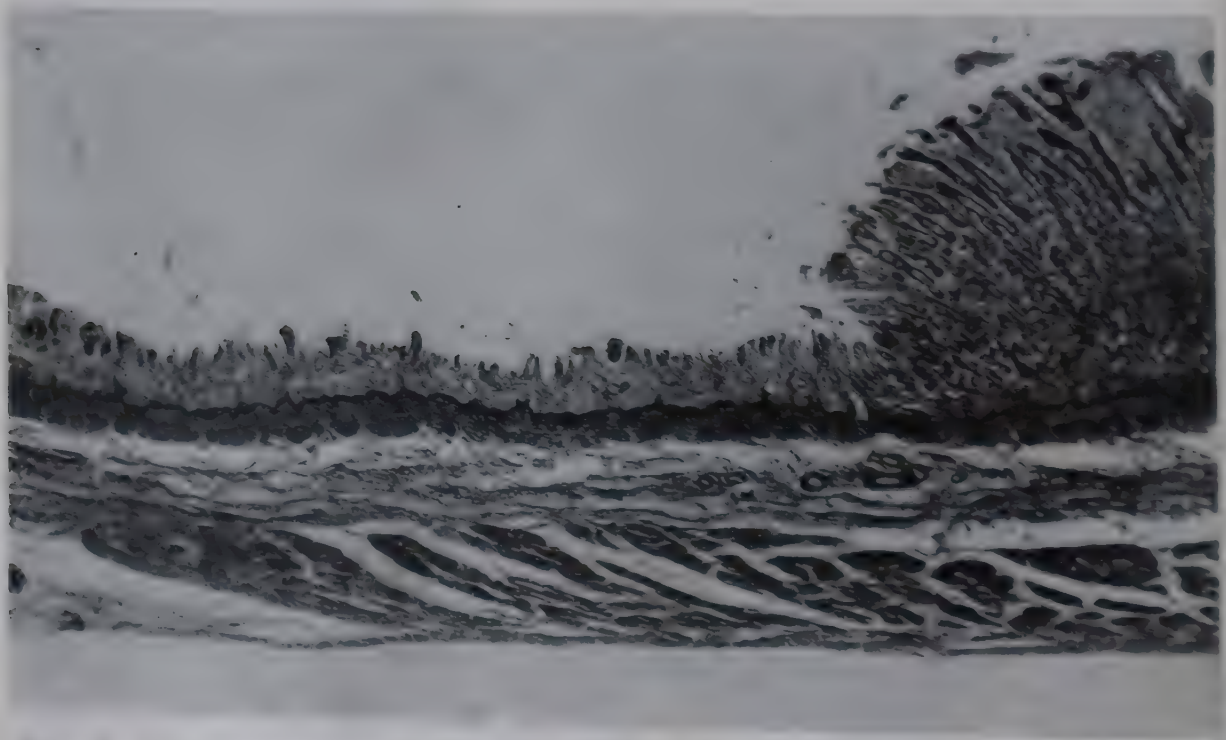


FIG. 6. A large erosion of the gastric mucosa. The muscularis mucosae is still covered by living cells.

to show signs of activity. Clearly, the anatomic classification of "active" and "inactive" ulcer depends on microscopic examination of the lesion, since it would hardly be accurate to state from the gross appearance of an ulcer whether, or to what extent, it exhibits polymorphonuclear neutrophilic "activity" in its floor. Moreover, it has not, to our knowledge, been asserted that histologic "activity" is always accompanied by symptoms, although the converse would be expected to occur.

The clinical usage of the terms "active" and "inactive" in reference to peptic ulcer appears to stem from the concept "once an ulcer, always an ulcer." The disease is considered to go on indefinitely once it is diagnosed, and the alternate periods of recurrence and remission are conveniently designated "active ulcer" and "inactive ulcer." There is no objection to such usage provided it is understood that the connotation is purely clinical.

"Round" and "simple" ulcer are designations used much less commonly today than in former times. They both refer to the nonspecific ulcer of the stomach, duodenum, or jejunum which has come to be designated "peptic" ulcer.

Acute and Chronic Ulcers of the Upper Digestive Tract

The two general types of benign ulcer of the stomach and duodenum, and of the jejunum after gastroenterostomy, are the acute and the chronic. Some authors include a third, intermediate type, the *subacute*.

The adjectives *acute*, *subacute*, and *chronic* may have many different medical connotations; as a rule, these terms imply a dual concept of time and severity, but sometimes only the time factor is implied and at other times only the severity. Clinically, the usual criteria of the acuteness or chronicity of a disease are the character of onset and the duration of symptoms. An acute process is relatively sudden in onset, short in its course, and usually severe; a chronic process is usually gradual in onset, sometimes develops from an acute process, is long in duration, and less severe in such signs and symptoms as fever and malaise. Pain may be of equal severity in both types.

The pathologic or histologic criterion for acuteness or chronicity is the nature of the cellular response in the tissues of the body, and it is this criterion which is properly applicable to gastroduodenal ulcer. This is true for two reasons. First, acute peptic ulcers attract little attention clinically, except in the relatively rare instance in which they perforate or bleed profusely; therefore, the diagnosis "acute ulcer" must be made almost always on anatomic grounds. Second, the diagnosis of an acute or chronic ulcer depends not so much on the duration of the lesion as it does on the stage

and nature of the inflammatory process in the margin and floor of the ulcer, as is evident from the following considerations.

Inflammation is the reaction of the body to injury or irritation. The necrotic tissue seen early in the center of the subsequent site of a gastric erosion or an acute ulcer is the result of some type of injury. The necrotic tissue is either sloughed off or digested by gastric juice. A local reaction occurs in the surrounding tissue, which constitutes an attempt to wall off and to repair the defect. One of the important features of the cellular reaction is a proliferation of fibroblasts, or cells which form connective tissue or a scar. This is called proliferative fibrosis. If considerable tissue has been destroyed, the lost tissue is theoretically replaced by the extra formation of fibrous connective tissue, and this is called *reparative fibrosis*. If the source of irritation is not promptly removed, proliferative fibrosis is increased; and since time is required for the proliferation of fibroblasts, the amount of fibrous tissue formed is a function of time as well as of the continued presence of an irritant. Hence, *the important difference between an acute and a chronic inflammatory process is the extent of connective tissue proliferation*, and this is likewise the important histologic difference between an acute and a chronic ulcer. A *subacute* inflammatory process is intermediate. Its recognition is unsatisfactory, because after proliferative fibrosis has started the acute stage is said to be passed and the chronic stage under way.



FIG. 7. An acute ulcer. Note that the defect in the mucosa has penetrated into the submucosa. The tissue at the margin of the ulcer was necrotic. Proliferation was not evident on microscopic examination.



FIG. 8. A chronic ulcer. The defect in the mucosa has almost penetrated to the serosa. The inflammatory process has penetrated the mucosa to cause adhesions. Dense connective tissue is present about the margin of the ulcer elevating the edge of the mucosa from the muscular layer.

In the case of an erosion, the defect in the mucosa is shallow (and usually small) and parts of the mucosal glands are present in the floor of the lesion (Figs. 5 and 6). Here, only a minimal proliferative fibrosis and no reparative fibrosis occur; the glands regenerate, and no scar results. *In the case of an acute ulcer*, the lesion penetrates through the muscularis mucosae (Fig. 7). By proliferative fibrosis, the floor of the defect is filled with granulation tissue; this is covered with proliferating epithelial cells, and since reparative fibrosis is minimal, the resulting scar is so small that it is difficult to find unless the acute ulcer was large. *In the case of a chronic ulcer*, healing has not occurred in the usual time or the local fibroblastic reaction to an irritant has been excessive. Hence, the chronic ulcer (Fig. 8) is characterized chiefly by the presence in its margin and floor of more connective tissue (and eosinophils) than is found in a healing or almost healed acute ulcer. The submucosal layer is thickened about the margin and for several millimeters beyond; the floor of the ulcer is thickened and the muscularis almost always is invaded. Proliferative fibrosis is followed by much reparative fibrosis, and a gross scar always results. If the healing is excessively delayed, the fibrous tissue becomes more closely packed and hard, yielding an *indurated or calloused chronic ulcer*. *A subacute ulcer* is intermediate between a healing acute ulcer and a definitely chronic ulcer. It represents an acute ulcer, the healing of which has been slightly retarded. The submucosa about the margin is somewhat thicker than in an acute healing ulcer; the margin is undermined in some regions and healing is present in others, and eosinophils are absent or few.

It is not an acute ulcer; yet one hesitates to call it a chronic ulcer. It is really an ulcer of "slight chronicity."

An experienced observer usually can distinguish between an acute and chronic ulcer by macroscopic examination. A histologic study usually is required to distinguish definitely between an erosion and an acute ulcer, and to determine the extent of fibrosis and healing, and of necrosis and degeneration in the base and margin of the ulcer. Even an experienced observer checks his macroscopic judgment of the gross specimen by histologic examination.

Usage of the Term "Peptic Ulcer"

The expression "peptic ulcer" has been widely used for several decades to refer to benign, nonspecific ulcers of the lower portion of the esophagus, of the stomach, of the duodenum, of the jejunum after gastroenterostomy, and of the Meckel's diverticulum with ectopic gastric mucosa.

The significance of this expression may be made clear by an outline of its historical background.

The acidity of gastric contents was demonstrated by Viridet (26) in 1692. Although Prout (31) in 1823 demonstrated that the acidity of gastric juice was due to HCl, this was disputed until 1852, when Bidder and Schmidt (27) proved the proposition. Claude Bernard (28), however, championed lactic acid as the acid in gastric juice as late as 1856. The discovery of the enzyme pepsin in gastric juice usually is credited to Schwann (29) who, in 1836, first used the word.

With these advances in physiologic knowledge in mind, Günsburg (23), in 1852, described a case of ulcer of the stomach associated with thrombosis of the gastric veins. He attributed the ulcer to "the corrosive action of gastric juice" and believed it was due to the excessive secretion of "free acid" caused by a disturbance of the vagus nerves. In the following year, Virchow (22), referring to Günsburg's report, proposed the theory that gastric ulcer was due to "the corrosive action of gastric juice," acting on an area of mucosa rendered susceptible by venous stasis caused by local spasm of the gastric musculature or to thrombosis or embolism of the blood supply of the ulcerated area. In 1860, Mueller (30) used the expression "Das corrosive Geschwür im Magen und Darmkanal," and, in 1863, Trier (24) published a monograph titled "Ulcus corrosivum Duodeni."

The expression "peptic ulcer" was first used by Quincke in 1882 (25). It has been adopted and widely used for two reasons. First, in a generic sense it refers appropriately to nonspecific ulcers found in those regions exposed to gastric juice. Second, in an etiologic sense it implies that the

ulcers are caused by the peptic activity of gastric juice. The use of the expression in the first or generic sense has not been disputed, and "peptic" is a much better term than the designations "round," "simple," "corrosive," and "perforating" which preceded its introduction. However, Shay (35) makes an excellent suggestion when he recommends the designation of the lesion according to its anatomic location. As he points out, we know today a great deal that earlier investigators did not know when they accepted the term "peptic" ulcer. Since we know that gastric and duodenal ulcer differ in their pathologic physiology, and possibly in their etiology, it would permit of greater clarity if they were referred to as though they were distinct entities. Hence the advantage of the specific terms "gastric," "duodenal," or "postoperative jejunal," or combinations of these when indicated.

Summary

The following terminology of ulcerative lesions of the upper gastrointestinal tract is recommended.

1. An *erosion* is a circumscribed mucosal defect which does not penetrate the muscularis mucosae.

2. An *ulcer* is a circumscribed defect which extends through the muscularis mucosae. (a) An acute ulcer is characterized by a margin and floor in which little or no connective tissue is present. (b) A chronic ulcer is characterized by an abundance of fibrous tissue in its margin and floor. A local eosinophilia is usually evident.

3. A *peptic ulcer* is a benign, nonspecific ulcer located in those portions of the alimentary tract bathed by gastric juice.

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OUTLINE OF CHAPTER 2

Physiology

I. Introduction
II. The Gastric Glands
  A. physiologic anatomy of the gastric glands
  B. composition of the secretion of the parietal cells
    1. Hydrochloric Acid
  C. composition of the nonparietal secretion
    1. Pepsin
    2. Mucus
III. Mechanisms of Gastric Secretion
  A. secretion of hydrochloric acid
    1. Periods and Phases of Gastric Secretion
      a. The Interdigestive Period of Secretion
      b. The Period of Digestive Secretion
        1. The Cephalic Phase
        2. The Gastric Phase
        3. The Intestinal Phase
    2. Humoral Mechanism in Gastric Secretion
      a. Evidence for a Humoral Mechanism
      b. Nature of the Humoral Agent
        1. Is the Humoral Agent Histamine?
        2. May Secretagogues on Being Absorbed into the Blood Be the Humoral Agent?
      c. Site of Origin of the Humoral Agent
    3. Inhibition of HCl Secretion
      a. Nervous Inhibition
      b. Enterogastrone
      c. Acid Inhibition
      d. Inhibition by Nausea
    4. Factors Affecting HCl Secretion Through Changes in the Blood and Blood Flow
  B. control of the secretion of pepsin
  C. control of the secretion of mucus
IV. Regulation of the Acidity of the Gastric Contents
  A. the major factors
  B. normal course of gastric secretion
V. Secretion of Brunner's Glands
VI. Motor Activities of the Stomach
VII. Summary

CHAPTER 2

Physiology

Introduction

The digestive action of HCl-pepsin must be considered among the destructive agents which may disturb the normal balance between the protective and destructive factors acting on the tissues of the stomach and upper intestine. This balance may be disturbed by (a) an increase in the quantity and duration of the secretion of HCl-pepsin, (b) a decrease in the secretion of fluids which dilute, neutralize, buffer, or inactivate HCl-pepsin, or (c) a decrease in cellular resistance to HCl-pepsin due to impaired nutrition or to the action of a cytotoxic agent.

It is appropriate, then, to inquire concerning the normal mechanisms which operate to prevent such imbalance. This chapter will be devoted therefore to a presentation of the normal physiologic control of pepsin-HCl secretion and the regulation of the acidity of the gastric contents. The regulation of gastric motility and the secretion of Brunner's glands will also be considered. A clear understanding of the normal processes is a requisite for an analysis of the aberrations which may occur in disease.

The Gastric Glands

Physiologic Anatomy of the Gastric Glands

In man, monkey, dog, cat, rabbit, and certain other mammals, the stomach is subdivided into two major areas, each characterized by the type of gastric gland it contains. The proximal two-thirds of the stomach is occupied by the proper gastric glands whose function, in general, is to produce the active digestive elements of the gastric juice (pepsin-HCl), while the distal third is provided with the pyloric glands, whose function is, in the main, the production of mucus.

There are, in addition, two minor zones which represent areas of transition between the major epithelial divisions. The first or upper of these minor zones is the cardiac zone, a narrow rim of mucous glands surrounding the esophageal orifice and separating esophageal from fundic mucous membrane. The second is the intermediate zone, a narrow strip of mixed

glands lying between the proper gastric glands and the pyloric glands. Figure 9 depicts the portion of the stomach occupied by these various gland types.

The various divisions of the gastric glands just outlined are all composed of the following four basic cell types in varying combinations and proportions: (a) surface epithelial cells, (b) neck chief cells, which are histologically identical with pyloric and cardiac gland cells, (c) parietal cells, and (d) body chief cells (Fig. 10). Each cell type produces a characteristic secretory product.

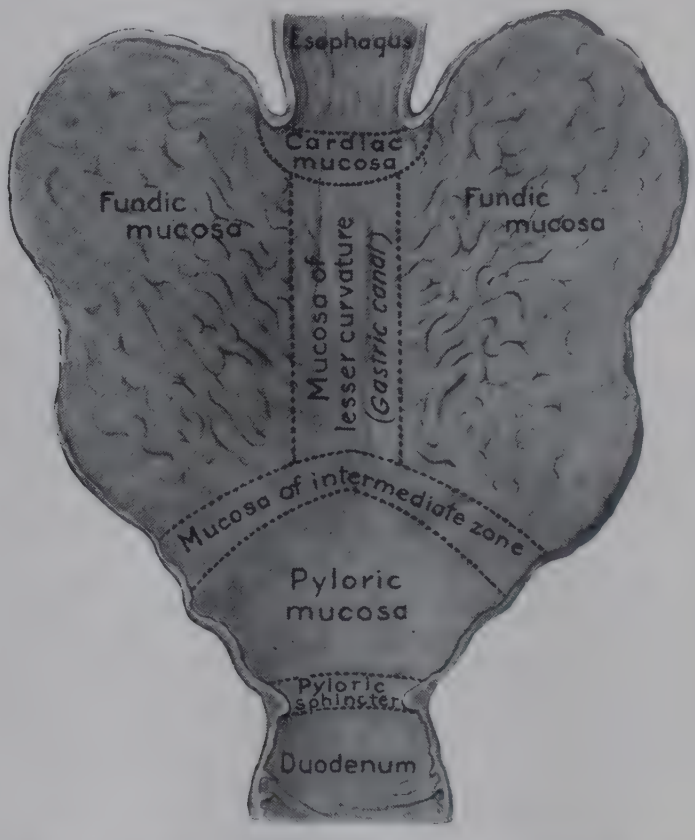


FIG. 9. Diagram showing the distribution of the various zones of the gastric mucosa.

The surface epithelial cells occur in all parts of the stomach; they line the entire surface of the stomach and the foveolae gastrica, or gastric pits, where they become continuous with the epithelium of the tubular glands. These cells contain mucinogen granules and contribute mucus (the "visible" mucus) to the gastric secretion.

The neck chief cells also occur in all parts of the stomach; in the fundic glands they are concentrated in the neck of the glands, whereas in the pyloric and cardiac parts they constitute the only cell type in the glands. The secretory product of the neck chief cells is a mucin whose character differs from that of the cells of the surface epithelium in being more soluble and less viscous.

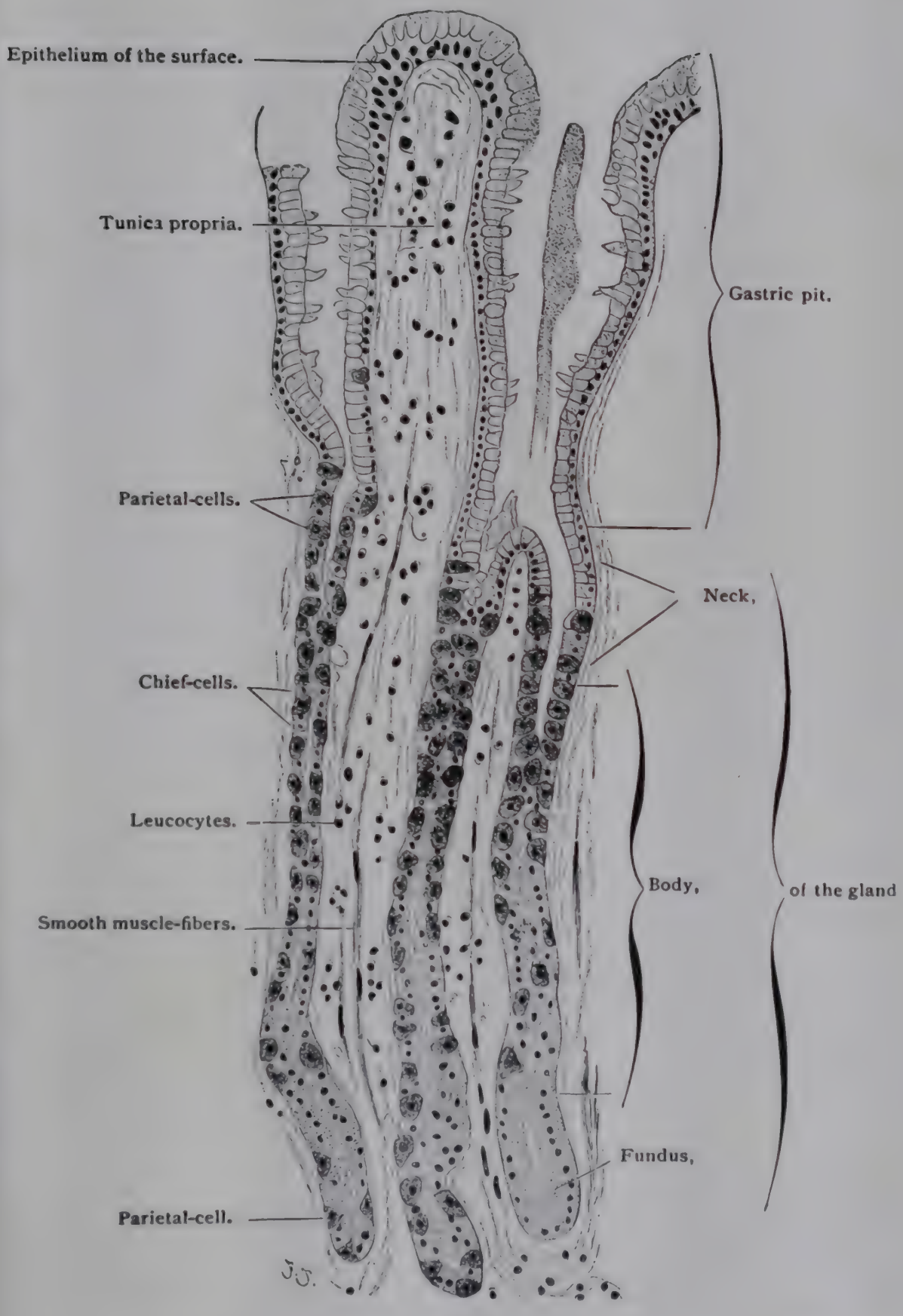


FIG. 10. Section of the fundic mucosa of the human stomach, showing the gastric glands. (Courtesy, Bremer and Weatherford: "Text-book of Histology," The Blakiston Company.)

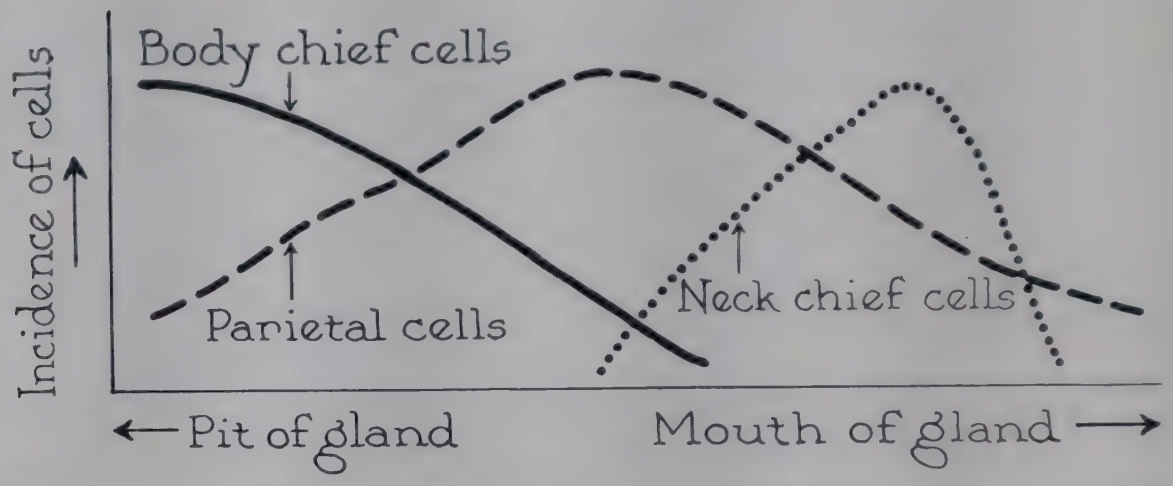


FIG. 11. The relative distribution of the different cells at the various levels of the gastric fundic glands.

Parietal cells and body chief cells occur only in the fundic part; it has been established that they secrete the hydrochloric acid and pepsin, respectively, of the gastric juice. The parietal cells lie not against the lumen but between the chief cells and the basement membrane. Though separated from the gland lumen by the chief cells, the parietal cells communicate with the lumen by means of delicate canaliculi which pass between the chief cells; the canaliculus is the terminal conduit of an extremely fine meshwork of channels within the parietal cell.

The distribution of the various cell types in the fundic glands is represented in figure 11.

Composition of the Secretion of the Parietal Cells

The exact composition of the secretion elaborated by the parietal cell can be arrived at only by computation, inasmuch as no means is available for the collection of parietal cell secretion unmixed with the secretion of nonparietal cells. In essence, the accumulated evidence concerning the composition of mammalian parietal cell secretion (not mixed gastric juice) indicates that it is relatively invariant, its composition being independent of rate of formation, strength of stimulus, or nature of stimulus.

Hydrochloric Acid

Since it is universally agreed that HCl is the characteristic and identifying product of the parietal cell, it follows that other substances secreted by this cell must vary in concentration in the gastric juice directly with the acidity. Substances not secreted by the parietal cell must vary in concentration in gastric juice inversely with the acidity. Substances whose concentration does not vary must be secreted in the same concentration by all the cells contributing to the gastric juice. Using this type of approach

(1) it may be concluded that pure parietal secretion consists of 166 m Eq./l. of chloride ion, 159 of hydrogen ion, and 7 of potassium ion. Some investigators (2) claim that only HCl and no neutral chloride is present in parietal secretion. Expressed in other terms, this concentration of HCl corresponds to 0.159 N, 159 clinical units, 5.8 mg. HCl/cc., 0.58 per cent HCl, pH 0.83. This theoretical maximum is, of course, never attained in the mixed gastric juice because some nonparietal secretion is always present. However, the acid concentration of the gastric juice may reach 150 m Eq./l. under strong histamine stimulation in dogs or humans.

It is to be noted that a solution of this composition is iso-osmotic with blood. Furthermore, if the osmotic pressure of the blood plasma is altered experimentally, the parietal secretion manifests corresponding deviations. In the formation of parietal secretion energy is required for two processes. The fact that the osmotic pressure of the blood and of the parietal secretion are the same means that energy for the performance of osmotic work is not required. The first energy requirement is that needed for overcoming viscosity in removing water from the blood and secreting it into the parietal secretion (3). The second energy requirement is the considerable amount needed to concentrate the chloride ion from the level which is present in blood to the level of the parietal secretion. The energy necessary for the concentration of the chloride ion probably is derived from the oxidation of glucose (1).

Composition of the Nonparietal Secretion

Analysis of the secretion of any individual cell other than the parietal cell has not been accomplished. Thus the only chemical analyses available on nonparietal secretion represent the mixed secretion of the body chief cells, neck chief cells, and surface epithelial cells. Using statistical and physico-chemical methods similar to those employed for the study of parietal secretion, it has been computed (4) that the mixed nonparietal secretion has an average ionic concentration as depicted in the graph in figure 12.

Unlike the parietal secretion, the mixed nonparietal secretion shows considerable variation in composition.

Pepsin

The chief enzyme of the gastric juice is the proteolytic principle, pepsin, which is secreted by the body chief cells of the fundic glands. An inactive precursor of pepsin called pepsinogen has been isolated in the form of a crystalline protein (5). Pepsinogen probably represents the immediate secretory product of the chief cells; unlike pepsin, it is relatively resistant to alkali and heat, losing little of its activity by short exposure to

pH values as high as 11 or to temperatures as high as 70° C., which cause immediate and irreversible inactivation of pepsin. If pepsinogen solutions are made more acid than pH 6, the pepsinogen is transformed into pepsin by an autocatalytic reaction, i.e., the product of the reaction, pepsin, catalyzes the further formation of pepsin from pepsinogen; thus in the acid gastric juice the enzyme is always present in the active form.

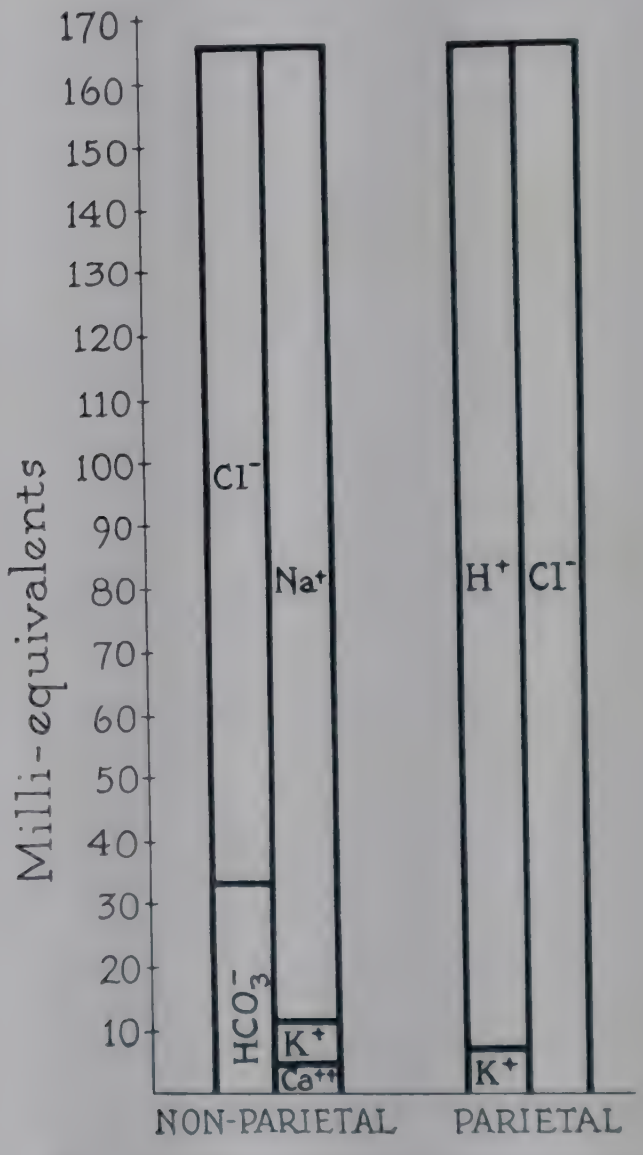


FIG. 12. The computed ionic concentration of the principal ions in the parietal and nonparietal secretions of the gastric gland.

Pepsin has also been isolated in the form of a crystalline protein (5) and has been shown to possess no nonprotein prosthetic groups. Recent studies indicate that crystalline pepsin is a solid solution of several forms of pepsin possessing different proteolytic potencies (6). The distinguishing characteristics of peptic digestion are that it (a) occurs only in distinctly

acid medium and (b) will not attack all peptide linkages indiscriminately but only those in which the amino groups are attached to aromatic amino acids. Thus the specificity of the enzyme is not concerned with the molecular size of the substrate protein but rather with the chemical configuration of the peptide bond. Complete peptic digestion results in a predominance of proteoses and peptones and relatively few amino acids and polypeptides. The optimum pH for the proteolytic activity of pepsin varies with the substrate protein but in general is about pH 2.

Mucus

The surface epithelial cells, the neck chief cells of the fundic glands, the pyloric gland cells, and the cardiac gland cells all secrete mucus. Two types of mucopolysaccharides have been isolated from gastric mucosa and gastric juice (40). One is an acid polysaccharide yielding upon hydrolysis sulfuric acid, acetic acid, hexosamine, and glucuronic acid. The other is a neutral polysaccharide which yields galactose and hexosamine on hydrolysis. The latter substance possesses powerful serologic properties and is able in high dilution to neutralize blood group specific antibodies. Other, as yet unidentified, mucopolysaccharides probably are present in gastric juice.

The mucus of gastric juice occurs in two forms, visible mucus and dissolved mucus; the former occurs as shreds or strands and may be separated from the gastric juice by filtration or centrifugation, while the dissolved mucus can be precipitated by the addition of 2 volumes of acetone or alcohol to the gastric juice. Visible mucus is believed to be secreted by the surface epithelial cells and dissolved mucus by the neck chief cells (7). Whether this division in the function of the two types of mucoid cells is valid is uncertain.

Mechanisms of Gastric Secretion

Secretion of Hydrochloric Acid

Periods and Phases of Gastric Secretion

The secretion of hydrochloric acid may be divided into the following periods and phases:

Period I. The period of interdigestive secretion
Period II. The period of digestive secretion
  Phase 1. The cephalic phase
    A. Unconditional reflexes
    B. Conditional reflexes

Phase 2. The gastric phase
- A. Mechanical distention
- B. Secretagogues

Phase 3. The intestinal phase
- A. Secretagogues

THE INTERDIGESTIVE PERIOD OF SECRETION. Does the stomach secrete hydrochloric acid in the absence of the stimuli which are responsible for acid secretion in response to a meal? When the fasting stomach is continuously drained by means of a stomach tube, the secretions recovered in man and in the dog almost always contain free HCl. Bloomfield (8) has applied the term "basal anacidity" to the condition in which there is an absence of free HCl in the fasting secretions of a person whose gastric glands are capable of responding with acid formation to histamine stimulation. According to Bloomfield, basal anacidity in man is a rare occurrence. The amount and acidity of the interdigestive secretion vary from person to person and from time to time in any one person. It is present in variable amounts throughout a fast of 40 days (9).

When a pouch has been fashioned from the stomach of a dog, interdigestive secretion of acid is still noted; this is true for subcutaneously autotransplanted pouches (devoid of all original extrinsic nerve and vascular supply), and all other types of experimental pouches which have been observed. Occasionally a gastric pouch will exhibit a basal anacidity; that is, it will secrete only in response to a meal or to pharmacologic stimulation. Such pouches, as a rule, are relatively refractory and secrete poorly even when strong stimulation is employed.

Thus it may be stated categorically that the normal human and canine stomach periodically secretes HCl during the interdigestive period. Unless this fact is recognized, the normal periodic interdigestive secretion might be interpreted erroneously as evidence of stimulation when an experimental procedure has been introduced. Therefore, in experimental work on man and animals the interdigestive secretion should be collected for an adequate period before any test procedure is instituted, and it should be kept in mind that a small increase or decrease may be spontaneous.

Pavlov (10) believed that the gastric glands do not secrete acid during the interdigestive period and that, if acid is present, it is due to the thought or odor of food. Essentially the same viewpoint is taken by Babkin (7) who, however, believes that other factors such as swallowing of saliva or regurgitation of duodenal juices, mechanical stimulation of the mucosa of the stomach, or food masses in the intestine also might contribute to interdigestive secretion. Psychic influences and the other factors mentioned can and probably do contribute to interdigestive secretion; however, none of

these factors can explain the occurrence of interdigestive secretion in the subcutaneously transplanted pouch unless they operate to produce a hormone. Thus, a basal secretion of acid occurs in the absence of any known mechanism for gastric secretion except possibly a humoral one. According to Babkin (7), vagal denervation of the gastric glands induces a continuous "paralytic" secretion of acid gastric juice; he considers this interdigestive secretion to be due to an abnormal mechanism of unknown nature, hence the designation "paralytic" secretion. The Pavlov-Babkin school holds that the interdigestive secretion noted in the vagally innervated stomach is due mainly to conditional reflexes, whereas the interdigestive secretion noted after vagal denervation ("paralytic" secretion) is due to an abnormal mechanism. This interpretation is based on the belief that after vagal denervation the stomach secretes HCl *continuously*, in contrast to the intermittent or phasic interdigestive secretion of HCl before vagotomy; and therein lies the crux of the misunderstanding. In our laboratory it has been a consistent observation over a quarter of a century that healthy dogs with vagally denervated gastric pouches secrete hydrochloric acid *intermittently* during the interdigestive period and *not* continuously.

The "paralytic" or continuous secretion of HCl after transection of the vagi has not been noted by us after the effects of the trauma of the operation have disappeared (7 to 21 days). It is true that continuous secretion of HCl sometimes occurs in gastric pouch dogs and we too consider this to be an abnormal state; but it occurs with no greater frequency and lasts no longer in dogs with vagally denervated pouches than in those with vagally innervated pouches. This abnormal continuous secretion of hydrochloric acid frequently occurs in dogs for several days after an operation; it also occurs when lesions such as erosions of the skin about the stoma of a pouch are present, in other conditions such as lactation, and in Mann-Williamson dogs (see p. 345).

The cause of the intermittent secretion of HCl during the interdigestive period is unknown. It is at least in part independent of vagal impulses and therefore of conditional reflexes. There is a tendency for the phasic increases in interdigestive secretion to be synchronous with the periods of hunger motility of the empty stomach and the same humoral factor may control both of these phenomena (11).

The Period of Digestive Secretion. This is the secretion which occurs in response to a meal. For clarity and simplicity this period is divided into three phases, the cephalic, the gastric, and the intestinal. Each phase is named to denote the region in which the stimuli are acting to excite gastric secretion. This, of course, is an arbitrary division, used only to assist in the analysis of the subject; the various phases overlap temporally.

The Cephalic Phase. This denotes that the stimuli are acting in the region of the head. The stimuli are the sight, smell, taste, and thought of food. They act through conditional and unconditional reflexes.

The *conditional reflex* (*"psychic" or "appetite"*) *secretion* of gastric juice is exemplified by the occurrence of secretion in response to the sight, smell, and thought of food. It occurs only in the presence of a desire for food, or an "appetite," and is dependent on the cerebral cortex for its development and operation.

The *unconditional reflex secretion* of gastric juice is demonstrated by "sham feeding" a decorticate dog with an esophageal fistula (12). Such a dog does not secrete in response to the sight and smell of food, but does secrete, after a brief fast, to "sham feeding," or to the taste and swallowing of food. Thus, the unconditional reflex secretion occurs in "the fasting state" on the adequate stimulation of the taste nerves, and it is independent of the cerebral cortex. The "fasting state" implies appetite, though it cannot be said that the decorticate dog has an appetite in the ordinary sense. However, the decorticate dog when hungry manifests "decorticate activity" which is abolished by feeding. So, those sensory or humoral factors which cause "decorticate activity" must facilitate the unconditional reflex secretory mechanism, since conditions which imply appetite or a need of food are requisite for the operation of both the conditional and unconditional reflex.

There is no good evidence that the excitation of nerves in the stomach and intestine unconditionally stimulate secretion through a long reflex to the medulla. But, the stimulation of such nerves evidently facilitates the unconditional reflex mechanism.

The *amount of juice* secreted during the cephalic phase in man is extremely variable. The volume of secretion (see Table 1) is affected by the appetite, the attitude of the subject, the acceptability of the food, and the time consumed in its ingestion, especially in the process of mastication. The duration of the secretion after cessation of eating also varies: it usually continues for 10 or 20 minutes.

The gastric juice of the cephalic phase is rich in all the elements secreted by the gastric glands. It has a high acidity, a high pepsin content, and a high concentration of dissolved and visible mucus.

The vagi contain the sole efferent excitatory nerves for the cephalic phase of gastric secretion. Section of the vagi or administration of atropine will abolish this phase. Electric stimulation of the vagi will, under appropriate experimental conditions, excite the formation of a copious amount of gastric juice similar in composition to that produced during the cephalic phase. Under vagal stimulation the zymogen granules of the chief cells and the mucinogen granules of the mucoid cells are depleted.

The Gastric Phase. This denotes that stimuli are acting in the stomach. The two types of stimuli acting in the stomach to excite the parietal cell secretion are (a) mechanical distention and (b) secretagogues, or chemical excitants. Of the latter, there are two types: (a) those naturally present in food, e.g., lean meat, liver, roast grains, whey of milk, and yeast, and (b) those which arise from the digestion of food, such as products of protein digestion and soaps.

Distention is the only adequate type of mechanical stimulation known. Rubbing the mucosa with a glass rod, a feather, or sand does not stimulate the secretion of acid. Beaumont observed secretion in response to distention, as did Pavlov. The latter attributed it to a psychic response; the dog thought food was being placed into his stomach, Pavlov reasoned. However, inasmuch as distention of a subcutaneously transplanted pouch stimulates secretion, the effect cannot be "psychic" or conditioned in origin. When a pouch of the entire stomach is distended with a balloon containing several hundred cubic centimeters of air, acid secretion appears after a latent period of 10 to 15 minutes; this secretion continues as long as the distending balloon is left in place and persists for approximately 10 or 20 minutes after its removal.

The *secretagogues* naturally present in foods such as meat are present in the extractives; that is, they are in the water-soluble nonprotein portion. Egg white is an example of a food which does not contain secretagogues naturally, but releases them on being digested. A solution of egg white perfused through the stomach does not stimulate; but if the egg white is digested with HCl-pepsin and then perfused, stimulation occurs. The chemical nature of the secretagogue in meat extract is not known; it is destroyed by vigorous boiling for 30 minutes. If perfusion is continued for one-half hour, the stomach secretes during the period of perfusion and continues to secrete above the control level for 1.5 hours and sometimes longer. Alcohol, 2 to 7 per cent, and histamine, 10 to 25 mg. in 50 cc. of water perfused through the stomach, stimulate the secretion of acid.

The Intestinal Phase. In this phase stimuli act in the intestine. Secretagogues are the only stimuli which excite gastric secretion on application to the intestine. Mild distension has no effect; undue distention or irritation of the intestine at first inhibits gastric secretion, probably reflexly. Further injury to the mucosa may produce stimulation, possibly by the release of histamine.

Secretagogues which act in the stomach also act in the intestine. Numerous other substances applied to the intestine stimulate gastric secretion, e.g., soaps, fatty acids, and peptones.

An estimate of the volume of secretion normally produced during the several phases of gastric secretion in man appears in Table 1.

Table 1

VOLUME OF GASTRIC JUICE DURING EACH PHASE

Period or Phase	*Amount (cc.)*
Interdigestive	30– 60 cc./hr.
Cephalic	50–150 cc./20 min.
Gastric	225–350 cc./5 hr.
Intestinal	200–300 cc./5 hr.

Humoral Mechanism in Gastric Secretion

EVIDENCE FOR A HUMORAL MECHANISM. When a meal not containing too much fat is fed to a dog with an autotransplanted pouch, hydrochloric acid is secreted by the pouch (13). This shows that a humoral mechanism is, at least in part, concerned in the gastric secretory response to a meal. Humoral stimulation of the gastric glands may be elicited by secretagogues acting in both the stomach and the intestine; the responsible agent in the two cases may or may not be similar or identical.

NATURE OF THE HUMORAL AGENT. The fact that an autotransplanted pouch secretes tells us nothing regarding the nature of the humoral agent. The humoral agent may be (a) histamine, (b) "gastrin," or an agent other than histamine (it may or may not be histamine-like), (c) secretagogues absorbed from the food in the stomach and intestine (the secretagogues may be absorbed unchanged or they may first be acted upon by the digestive secretions).

Is the Humoral Agent Histamine? Edkins (14) and others showed that the subcutaneous injection of acid extracts of pyloric mucosa would stimulate gastric secretion. He called the active principle "gastrin." It was soon shown that a gastrin was present in extracts of fundic mucosa and of numerous other tissues. Since those tissue extracts which stimulated gastric secretion also depressed blood pressure, it was suspected that the active constituent of the extracts was histamine or a histamine-like substance. This contention was supported by the following findings (15): (a) The gastric secretory and vasodepressor activity of the extracts is destroyed by histaminase, (b) histamine was isolated from such extracts as a crystalline sulfate and picrate, (c) the secretory and vasodepressor activities, expressed as a ratio, remained relatively constant in all fractions including the final step of crystallization. This evidence showed that Edkins' "gastrin" is histamine; but it does not warrant the conclusion that histamine is the gastric hormone. All that can be deduced is that either histamine is the gastric hormone, or that the true gastric hormone was not contained in these extracts, or that there is no gastric hormone.

Ordinary doses (0.5–1.0 mg.) of histamine administered subcutaneously provoke abundant gastric secretion without causing a detectable increase in the blood histamine level. Thus the parietal cells are more sensitive to histamine than is the method for measuring histamine in the blood. When histamine is infused slowly intravenously, it stimulates gastric secretion without causing vasodilatation or a fall in blood pressure. Since atropine (1 mg.) during the period of its maximum effect abolishes the secretory response to a meal but not to injected histamine, it must be concluded that if histamine is the normal humoral agent then atropine must prevent it from being formed. Komarov (38) has reported the presence of a non-histamine-like secretagogue in extracts of pyloric mucosa, active on parenteral administration. Uvnäs (45) and Harper (29) have confirmed Komarov's findings.

May Secretagogues on Being Absorbed into the Blood Be the Humoral Agent? Liver concentrates prepared for the treatment of pernicious anemia contain most of the secretagogic activity of liver. When such an extract, freed of vasodepressor material, is injected slowly intravenously, gastric secretion is stimulated. This shows that secretagogues could stimulate if they should be absorbed as such from the stomach and intestine. However, it requires 2 to 5 times as much secretagogue to stimulate gastric secretion when administered intravenously as when applied to the gastric mucosa (16). Therefore, at least part of the response to secretagogues is due either to (a) the alteration of the secretagogue by the gastric juice before it is absorbed or (b) the elaboration of a hormone. The first possibility is unlikely because preliminary incubation of the extract with gastric juice does not increase its effectiveness in stimulating gastric secretion when administered intravenously (17); on the other hand, evidence obtained by the use of procaine in dogs with two stomach pouches (v.i.) indicates that the contact of secretagogues with the gastric mucosa causes a hormone to be released.

Site of Origin of the Humoral Agent. In an animal which has been provided with both a transplanted pouch and a pouch of the remainder of the stomach, perfusion of the main pouch causes the transplant to secrete. Furthermore, on feeding such a "two pouch" animal (the food goes directly into the intestine because the animal has an esophagoduodenostomy) the transplant will secrete; similarly, application of liver extract to a Thiry fistula causes the transplant to secrete. Thus, a humoral agent is involved in the action of secretagogues in both the stomach and the intestine (18, 19).

Distention of the main stomach does not ordinarily cause the transplant to secrete (18); however, in a dog with a very large subcutaneously trans-

planted pouch, secretion of acid by the transplant has been observed in response to distention of the pouch of the remainder of the stomach (19).

A pouch of the entire stomach secretes less acid in response to secretagogues when the pyloric portion is removed (21). After resection of the pyloric part of the main pouch in a "two pouch" dog, the presence of secretagogues in the remainder of the main pouch causes the transplant to secrete less than before pylorectomy (18). Thus the pyloric mucosa contributes to, but is not the sole site of origin of, the humoral agent arising in the stomach.

Inhibition of HCl Secretion

NERVOUS INHIBITION. The sympathetic nerves are believed to convey the impulses responsible for the inhibition of HCl secretion in the presence of emotions such as fear and anger (22). The sympathetic nerves are known to mediate the inhibition of gastric motility under these circumstances. There are also inhibitory secretory nerves in the vagi, since, following vagotomy, it is only after these nerves degenerate that the excitatory secretory nerves in the vagi can be demonstrated readily by electric stimulation.

ENTEROGASTRONE. When neutral fat or sugars are present in sufficient concentration (10 per cent by volume or higher) in the upper small intestine, gastric motility and secretion are markedly depressed. The presence of these substances in the stomach will not elicit this inhibitory effect. The inhibition of motility and HCl secretion has been demonstrated to occur in a subcutaneously transplanted gastric pouch; the effect is, therefore, humorally transmitted. The possibility that absorbed products of digestion constitute the humoral agent has been ruled out by demonstrating that the introduction of olive oil or cream into the intestine of a dog with an autotransplanted pouch inhibits the secretion of the pouch, whereas the intravenous administration of fatty chyle, soap, and emulsified fat does not.

Therefore the humoral agent is a hormone, or according to Schaefer's terminology, a chalone formed by the action of neutral fat or sugars on the mucosal cells of the upper small intestine; it enters the blood and is conveyed to the stomach where it exerts an inhibitory effect on muscular and parietal cell activity. A substance has been prepared from upper intestinal mucosa, which upon intravenous injection reproduces some of the action of fat in the intestine. For instance, it can inhibit gastric secretion stimulated by a meal, sham feeding, or the injection of insulin, histamine, or pilocarpine. The active principle of these extracts has been given the name *enterogastrone*. The intravenous administration of 50 mg. of purified enterogastrone concentrate in the dog will reduce by about 50 per cent the acid

secretory response to an ordinary dose of histamine (23). In man the inhibition caused by the introduction of 40 cc. of olive oil into the duodenum lasts for 1.5 to 2.5 hours. The sensitivity to the inhibitory effect of fat upon gastric evacuation varies from person to person. About 85 per cent of normal individuals show delay in gastric emptying when fat composes 8 per cent of the wet weight of a mixed meal (41). A very high concentration of unemulsified fat in the intestine may cause increased motility of the large and small intestine with the passage of unchanged fat per anum. Fatty acids and soaps, as well as neutral fat, can produce inhibition of gastric motility.

When a meal consisting of about 80 per cent meat and 20 per cent fat is ingested, the secretory response is very low during the first hours but rises gradually during the later hours. This secondary rise in gastric secretion following a meal high in fat has been attributed to the stimulating action of soaps formed in the intestine during the digestion of fat (24). However, although soaps in the intestine are capable of stimulating gastric secretion, it is conjectural whether they are normally present in sufficient concentration to account for the secondary rise in gastric secretion following a meal containing fat. It is more probable that this secondary rise is due to the withdrawal of the inhibitory effect of the fat.

Acid Inhibition. This expression is used to indicate that the presence of acid in the stomach or intestine inhibits gastric secretion. Acid inhibition occurs only when a certain threshold of acidity has been reached and it operates only against certain stimuli. Acid (0.36 per cent) in the stomach inhibits the action of secretagogues in the stomach, but not that of secretagogues in the intestine, while acid in the intestine inhibits the action of secretagogues in the stomach or the intestine. When the stimulus is strong, as when secretagogues are acting simultaneously in the stomach and intestine, or when histamine is the stimulant, acid in the intestine does not inhibit. The cephalic phase of gastric secretion is refractory to the inhibitory action of acid in the stomach or duodenum (25, 26).

Prolonged action of strong acid on the intestinal mucosa may stimulate gastric secretion. For example, the continuous perfusion of acid (0.36 per cent) through a Thiry fistula of the duodenum and jejunum will usually cause stimulation of gastric secretion after a latent period of about 45 minutes. In this case the mucosa has been injured by the acid. The feeding of a meal after such an experiment sometimes results in an abnormally high secretory response of a Pavlov pouch. Repeated daily perfusion of the Thiry fistula with acid may cause a hypernormal interdigestive secretion (27). It is possible that irritation of the mucosa with acid or any other noxious agent may cause the release of histamine or a histamine-like substance, as does irritation of the skin.

Inhibition by Nausea. Nausea inhibits gastric secretion by a mechanism which is independent of vagus and splanchnic nerves (20).

Factors Affecting HCl Secretion Through Changes in the Blood and Blood Flow

In addition to the specific excitatory and inhibitory influences, many systemic variations influence acid secretion. It is well known that febrile conditions in general produce temporary achlorhydria or hypochlorhydria. Bacterial pyrogens as well as other pyrogenic substances can inhibit gastric secretion and motility. A profound fall in blood pressure, anoxia, acapnia, hypochloremia, anhydremia, or severe anemia all produce a depression of HCl secretion.

Four types of anoxia are recognized: anemic, anoxic, stagnant, and histotoxic. Anemic anoxia refers to a deficiency of functioning hemoglobin. Anoxic anoxia refers to the condition in which O_2 tension in the arterial blood is low or the hemoglobin is not fully saturated with oxygen. Stagnant anoxia refers to anoxia due to a decrease in circulatory rate. Histotoxic anoxia refers to a condition in the cells in which they are not able to utilize oxygen, as in cyanide poisoning.

Anoxic anoxia does not affect the continuous or interdigestive secretion even when the subject (dog) is exposed to an altitude of 18,000 feet which usually yields a blood-oxygen saturation of from 65 to 75 per cent. The response to a meal containing meat is depressed when the blood oxygen saturation is approximately 75 to 80 per cent. Anemic anoxia depresses the gastric secretory response to a test-meal when the hemoglobin falls below 12 Gm. per 100 cc. The amount of stagnant anoxia required to depress and abolish gastric secretion has not been studied (39). It is well known among laboratory workers that a decided fall in blood pressure, or stasis to the extent that marked cyanosis of the gastric mucosa occurs, abolishes gastric secretion. On the other hand, the administration of excessive amounts of saline by clysis stimulates HCl secretion. General body hydration (e.g., as measured by leg volume) has been correlated with the volume and acidity of the fasting gastric contents in the human (28). Physical and chemical trauma directly to the gastric mucosa, such as x-ray, hot (70° C.) water, saturated salt solution, and hydrogen peroxide reduce acid secretion by damaging the parietal cells; the zymogenic cells are much less susceptible to these agents.

The effect on gastric secretion of sodium bicarbonate administered by mouth has been controversial since Claude Bernard first observed that it stimulated secretion. Without presenting an analysis of the confused literature at this time it may be stated that the best evidence indicates that sodium bicarbonate ingestion in ordinary doses probably results

in an increase in the concentration and total output of HCl in response to a meal stimulus (29).

Control of the Secretion of Pepsin

Pepsin is secreted continuously. Unlike HCl, it is constantly present in gastric juice although it cannot, of course, act in the absence of acid. Thus pepsin is constantly being released into the stomach even in the absence of specific stimuli for its secretion. During the interdigestive period, when only small amounts of pepsin are being secreted, pepsin is stored in the body chief cells, as evidenced by the accumulation of zymogen granules in these cells.

The major stimulus for pepsin secretion is vagal nervous impulses. Sham feeding, electric stimulation of the vagus, and insulin (which stimulates gastric secretion by hypoglycemic excitation of the vagal center) produce a gastric juice very rich in pepsin; similarly, parasympathomimetic drugs such as pilocarpine and acetylcholine are strong excitants of pepsin secretion. Histamine evokes a secretion of gastric juice of low pepsin concentration; however, the total output of pepsin is increased by histamine, and larger doses of histamine stimulate increased enzyme output (30). So histamine may be regarded as a true stimulant of pepsin secretion, though a weak one.

The pepsin content of gastric juice secreted in response to a hormonal type of stimulus is low like that of histamine-stimulated juice (31). There is some evidence that acid and secretagogues acting in the intestine stimulate pepsin secretion (32) and certain impure extracts of intestinal mucosa (secretin preparations) contain a pepsin-stimulating principle (33).

The concentration of pepsin in the gastric contents is highest in the first hour of digestion and declines as the volume of gastric juice increases; in the later stages of digestion, when the volume of gastric juice is diminishing, the peptic activity tends to increase. These relations are due to the independent control of the secretion of HCl and pepsin. Most of the water of gastric juice is secreted by the parietal cell along with HCl; therefore if only the *concentration* of pepsin rather than the total output is studied, concomitant changes in parietal secretion may mask changes in pepsin secretion.

Pepsin is a preformed secretory product and cannot be elaborated as rapidly as it is secreted during the early phases of active secretion. Therefore, all stimulants of pepsin secretion produce an initial "spurt," during which stored pepsin is rapidly extruded, followed by a leveling off to a rate of secretion characteristic of the stimulant which is acting.

Depletion of pepsin cannot be accomplished even by prolonged and intense stimulation (34); the rate of anabolism is probably dependent on

the rate of extrusion. *No instance has been recorded in which pepsin is absent from gastric juice which contains hydrochloric acid.*

The concentration of pepsin in human gastric juice is five to ten times as great as in the dog or cat. The average human gastric juice stimulated by histamine has a peptic power equivalent to that of a solution containing 0.5 to 1.0 mg. of crystalline pepsin per cubic centimeter.

Although it has been demonstrated that most or all of the inhibition of motility and HCl secretion caused by fat can be accounted for by the action of the hormonal agent enterogastrone, in the case of inhibition of pepsin secretion by fat in the intestine the vagus nerves are involved (35). This effect is due to true inhibitory fibers in the vagus and not merely to decrease in tonic excitatory impulses.

Control of the Secretion of Mucus

There is no good evidence showing that the extrinsic nerves play a significant role in the control of mucus secretion. The major stimuli for mucus secretion are the local action of chemical and mechanical irritants, acting either directly upon the cells or through local reflex arcs. Vagal stimulation produces an increase in mucus production but this is probably secondary to mechanical stimulation in the form of rubbing of the mucosal folds together as a result of the increased motility accompanying vagal stimulation. Pilocarpine does not cause an increase in mucus secretion by a pouch of the pyloric part of the stomach when mechanical stimulation secondary to motility is prevented (36).

Mucus is secreted continuously. Increased mucus production occurs in response to mechanical stimuli such as a rough diet and to chemical stimuli such as hydrochloric acid, alcohol, and spices.

Regulation of the Acidity of the Gastric Contents

The Major Factors

The acid in the gastric contents is supplied by a secretion (the parietal cell secretion) which is relatively invariant in acid content. Therefore the acidity of the mixed gastric contents can only be the result of two general major factors:

A. The rate of secretion and total quantity of parietal secretion as regulated by all the processes discussed under the mechanisms of gastric secretory stimulation and inhibition.
B. The removal or alteration of parietal secretion by
   1. the emptying of the stomach,
   2. the back diffusion of acid and water into the blood across the gastric mucosa (this process plays an insignificant role),

3. the neutralization, dilution, and buffering of HCl by
   a. ingested food
   b. nonparietal secretion (mucus, dissolved mucus, secretion of peptic cells),
   c. extra-gastric digestive juices which may enter the stomach, such as saliva, intestinal juices (succus entericus, Brunner's gland juice, bile, pancreatic juice), and esophageal mucus (insignificant in quantity).

Normal Course of Gastric Secretion

The gastric secretory response to a meal depends upon the quantity and chemical nature of the food and the relish with which it is eaten. Although a relatively large amount of parietal secretion with an acid concentration of 159 C.U. is secreted during a meal, the acidity of the gastric contents usually does not rise above 50 C.U., though in some "normal" persons the acidity may amount to as much as 120 C.U. These relations are depicted graphically in figure 13.

After the dilution and neutralization caused by the meal is ended, the acidity of the gastric contents rises as a result of the secretion of acid in response to the meal. However, it does not ordinarily rise excessively because the stimuli for secretion are withdrawn. The cephalic phase ends soon after ingestion of the meal, the gastric phase when the stomach empties, and the intestinal phase when absorption is completed. *The withdrawal of stimuli is the main* reason for falling off of the secretory curve. If the withdrawal of stimulation does not suffice to check an inordinate rise in acid concentration, the self-regulatory mechanisms or "safety-valves" are called into play; namely, acid inhibition and enterogastric

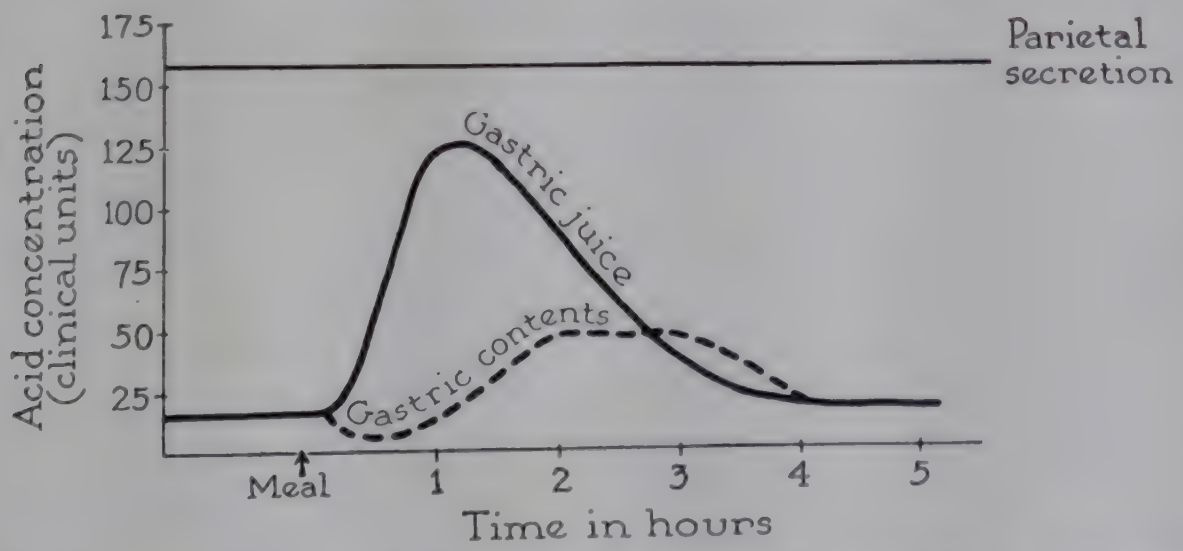


Fig. 13. The relative acid concentration of parietal secretion, gastric juice, and gastric contents in response to a meal.

regurgitation. Acid inhibition has been discussed above. Enterogastric regurgitation occurs when the acidity of the gastric or duodenal contents reaches a threshold which varies from person to person. Although the extrinsic nerves facilitate the mechanism, enterogastric regurgitation can be mediated by the intrinsic nervous plexus alone (37). The basic mechanism of the phenomenon involves inhibition of gastric tone creating a pressure gradient in favor of the movement of material from the duodenum into the stomach. Enterogastric regurgitation is a frequent and normal occurrence near the end of a meal. From 50 to 70 per cent of adults have bile in the gastric residuum before breakfast.

The rise and fall in acid concentration of the mixed gastric juice (parietal plus nonparietal secretions) is due entirely to the changing proportion of parietal to nonparietal secretion. Most of the water in gastric juice is secreted by the parietal cells; therefore the acid concentration of the mixed gastric juice varies directly, but not linearly, with the volume rate of secretion. When the rate of parietal secretion is low, as it is at the beginning and toward the end of a period of stimulation, the parietal secretion represents a smaller portion of the mixed gastric juice and the acidity is thus lower. During the height of secretion, the parietal component forms a very high percentage of the gastric juice and the acid concentration of the gastric juice therefore tends to approach the value of parietal secretion. In general, the variation in secretory rate between the digestive and interdigestive period is not nearly so great for the nonparietal secretion as it is for the parietal secretion.

Secretion of Brunner's Glands

Brunner's glands or the duodenal glands occur in the duodenum and to a lesser extent in the upper jejunum. In the first few centimeters of the duodenum the glands are located in both the region above and the region below the muscularis mucosae. Below this point these glands are confined to the region below the muscularis mucosae and empty into the bases of the crypts of Lieberkuhn.

From the pyloric sphincter to the papilla of Vater the duodenal glands are continuous and numerous in man. Below the papilla of Vater the glands become progressively more sparsely distributed and in the upper jejunum only a few small islands of these glands are to be found.

Histologically the duodenal glands are indistinguishable from the pyloric glands; both consist of "mucoid" type cells.

The secretion of these glands is a clear, slightly viscous fluid containing a moderate amount of clumped or visible mucus. It is alkaline in reaction and each cubic centimeter of juice obtained from the dog is capable of neutralizing, on the average, 0.3 cc. of 0.1N hydrochloric acid. A very

significant amount of neutralization of gastric acid is accomplished by the duodenal gland secretion because it is abundantly produced in response to the presence of acid in the duodenum.

The amount of juice secreted by the duodenal glands is noteworthy. In the dog, a basal secretion of from a few tenths to 2 cc. per hour occurs and this may rise as high as 20 cc. per hour in response to feeding a meal.

The duodenal glands are under both nervous and hormonal control. The vagus nerves stimulate and the sympathetics inhibit secretory activity. A hormone which stimulates duodenal gland secretion has also been shown to exist. When the Brunner gland area is extrinsically denervated by transplantation to the skin the secretory response to the ingestion of a meal still occurs (42). A substance can be extracted from the intestinal mucosa which, upon intravenous injection, stimulates the flow of Brunner's gland juice. The active principle of these extracts is probably not secretin (43).

Motor Activities of the Stomach

The stomach manifests contractile activity both when it is empty and when it is filled. The movements of the empty stomach, the hunger contractions, when they are of sufficient strength, give rise to the characteristic gnawing tension or dull pain in the epigastric region known as "hunger pangs." Although the hunger pangs are caused by the hunger contractions of the stomach, the other sensations associated with the hunger state such as the feeling of emptiness, lassitude, weakness, or faintness can occur independently of gastric contractions.

The hunger contractions are peristaltic in nature. They start in the lower portion of the esophagus or the cardiac portion of the stomach and sweep with augmenting strength over the entire stomach and die out in the duodenum.

Hunger contractions develop in the empty stomach at a variable interval after gastric emptying. This latent period, the vigor of the contractions and the relative duration of hunger and rest periods are related to the metabolic needs of the individual (age, length of fast, metabolic rate, etc.). Usually a 30- to 45-minute period of activity alternates with a 30- to 60-minute rest period.

The motor activities of the stomach during digestion consist of the reception of a meal, the mixing of the food with the gastric juice, maceration and fragmentation of the food particles, and discharge of the chyme into the duodenum.

Two mechanisms operate to prevent any marked increase in intragastric pressure when food enters the stomach. The first is receptive relaxation, a reflex inhibition of gastric tone which may be initiated

either by the passage of a peristaltic wave from the esophagus onto the stomach or by merely seeing, smelling, or tasting food. The second mechanism is metrostasis, or the ability of a hollow viscus with walls composed of smooth muscle to change the resting length of its fibers without a significant change in tone or pressure exerted on the contents.

The greater portion of a meal is held in the reservoir portion of the stomach, the "hopper" or fundic portion with relatively thin muscular walls. Here it undergoes but little mixing, so that the portions tend to persist for some time as discrete layers. Infrequent, feeble peristaltic waves pass over this region. Periodically a portion of the mass is forced into the "mill" or pyloric antrum where it is mixed and broken up into fragments by the powerful peristaltic waves which pass toward the sphincter. The contractions starting near the antrum require approximately 30 seconds to reach the pylorus. Those starting near the cardia require one to three minutes. From one to four waves can be seen on the stomach at one time during gastric evacuation.

The major factors regulating the rate of gastric evacuation are the antral tonus and antral contraction waves, the activity of the pyloric sphincter, and the character of the food. Recent studies have directed attention away from the pyloric sphincter as the major factor in the control of normal gastric emptying and have demonstrated that the most important factor is the action of the antral pump (44). Emptying of the stomach is governed chiefly by the gradient of pressure between the pyloric antrum and the duodenal bulb as determined by the tone and peristaltic activity of these regions and whether the waves persist or tend to die out as they approach the sphincter. When the antral wave travels to the sphincter and completely occludes the lumen as it progresses, practically all the material ahead of the wave is expelled, but when weaker waves occur much of the chyme returns to the body of the stomach. The portion expelled is chiefly the thinner material; larger lumps "bounce" back into the stomach when they reach the pyloric sphincter. During most of the emptying period the waves begin in the region of the incisura angularis, but as emptying nears completion the waves start higher in the gastric body and cardia.

The major stimulus for the peristaltic waves that empty the stomach is the distention of the stomach by the food. Thus, a large meal produces a more rapid evacuation rate than a small one.

As the first portions of gastric chyme enter the duodenum they exert an influence on the further emptying of the stomach. As Quigley (44) states: "if the sample proves satisfactory, the remainder leaves the stomach rapidly; unsuitable material initiates reactions from the duodenum which temporarily retard further gastric evacuation." In other words, one of the

most important factors in regulating the emptying of the stomach is the suppression of gastric motility by regulatory mechanisms operating from the upper intestine. Mere distention by an indifferent substance or the presence of small quantities of more specific substances such as fats, hydrochloric acid, protein split products, sugars, or hypertonic solutions causes inhibition of antral peristaltic waves and slows gastric emptying. These inhibitory influences from the upper intestine are mediated by both nervous and hormonal mechanisms. The nervous inhibition is known as the enterogastric reflex and operates chiefly, but not exclusively, by way of the vagus nerve. The hormonal inhibition is due to the release of enterogastrone by the intestinal mucosa when fats or sugars of sufficient concentration are in contact with it. Inhibition of gastric secretion by the enterogastrone mechanism has already been discussed. It is not known whether the same hormonal agent is responsible for both secretory and motor inhibition.

Summary

This entire chapter is considered to be a summary of our knowledge.

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CHAPTER 3

Incidence of Ulcer in Lower Animals

Introduction

One of the important prerequisites to a proper evaluation of the results of procedures designed to produce peptic ulcer experimentally is a knowledge of the frequency with which such lesions occur spontaneously in the animals under study. Considerable information is available in the literature on this point.

Dogs

Turck (16) examined 271 dogs killed at the city pound in Chicago and failed to find a single instance of ulcer. Mann (9) found no lesions of the gastric mucosa in 200 autopsies of dogs and cats. Greggio (3) stated that, in eight years of autopsies on dogs and rabbits, he had never been able to demonstrate a lesion that could be considered an ulcer. An undesignated number of dogs killed by gas was examined by Rosenow (13), who found that the incidence of ulcer was 1 in 40. Rogoff and Stewart (12) found no ulcers in 17 dogs sacrificed as controls for their adrenalectomy experiments. In 100 normal dogs autopsied immediately after death, Battaglia (1) reported no ulcers in the stomach or duodenum. Overgaard (11) thinks that spontaneous ulcer formation in dogs is much more frequent than has hitherto been believed; autopsy of 1,000 dogs in the Pathologic-Anatomic Institute at Copenhagen revealed gastric ulcer in 5 cases and duodenal ulcer in 3 cases. Keller (7) examined the digestive tracts of nearly 150 dogs; in 10 or 12 instances, characteristic shallow, round, hemorrhagic craters (acute lesions) were observed in the body of the stomach and in the pylorus. These occurred in slightly thin animals having signs of infection of the respiratory tract; in no instance was any sign of a gross defect encountered in the mucosa of the duodenum. Volini, Widenhorn, and De Feo (17) found no evidence of ulcers in the stomach or duodenum of 55 dogs. We (6) did not find a single case of chronic ulcer in healthy dogs in 1,000 consecutive necropsies.

Cows and Sheep

Rosenow (13) reported that the incidence of ulcer in cows and sheep was 1 in 60, but this varied with the season; more lesions were noted during

the latter part of the winter and early spring months when the sheep were eating coarse, dry foods, whereas during the summer and fall, when the animals were in pasture, the ulcers healed, as was evident from the presence of large scars.

Swine

During 1926–1930, we examined the stomachs of 1,000 swine at the abattoirs in Chicago without finding even an erosion. The animals were all healthy, since a rigid inspection is exercised before the animal reaches the killing floor and before the stomach is available for examination. Ulcers of the stomach do apparently occur in swine that are ill; Kernkamp (19) found 18 instances of chronic gastric ulcer in 754 swine autopsied because of obvious illness.

Rats

Singer (14) reported ulcers in 8 per cent of 200 well-kept control rats, whereas McCarrison (8) found no macroscopic evidence of disease in the stomachs of 1,189 albino rats; Howes and Vivier (5) autopsied 75 rats and found no lesions.

Rabbits

Ophüls (10) states, without giving any figures, that "chronic ulcers of the stomach do not occur spontaneously in rabbits." We (2) examined the stomachs of more than 100 rabbits without noting an instance of chronic ulcer.

Guinea Pigs

Routine examinations made by Smith and McConkey (15) on 1,000 guinea pigs failed to reveal a single instance of peptic ulcer.

Monkeys

Hoff and Sheehan (4) examined a control series of 50 monkeys subjected to various nonspecific types of cerebral lesions, and found no peptic ulcers. It is their opinion that "true peptic ulceration is a very rare occurrence in normal monkeys." The same conclusion is reached by Watts and Fulton (18), who found no consistent alterations in the stomach and intestine of 300 monkeys with various cortical and spinal lesions made for other studies. Kennard (25), however, reported two gastric ulcers in a series of 138 monkeys, mostly rhesus, only 19 of which were fully mature. These animals, too, had been used for experiments on the central nervous system.

Seals

Schroeder and Wegeforth (24) have published important observations regarding the spontaneous occurrence of chronic gastric ulcer in seals.

During routine necropsies performed at the zoo of the San Diego Zoological Society, they found that a majority of the recently captured animals had chronic gastric ulcers which were infested with a nematode. In a special study undertaken to ascertain the incidence of gastric ulcer in seals in their natural habitat, which in this instance was the Lower California group of islands, they examined 46 specimens (elephant seal, California sea lion, Harbor seal, and Galapago Fur seal) and in every case found gastric lesions varying from hemorrhagic erosions to chronic indurated gastric ulcers with imbedded parasites (Figs. 14, 15). This chronic ulcer is deep and punched out and its margin is elevated by a marked proliferation of connective tissue.

The etiology of these lesions has been adequately explained as follows: the seal, after eating, ordinarily swallows stones 1.0 to 1.5 inches in diameter, presumably to facilitate trituration since the stones are later regurgi-

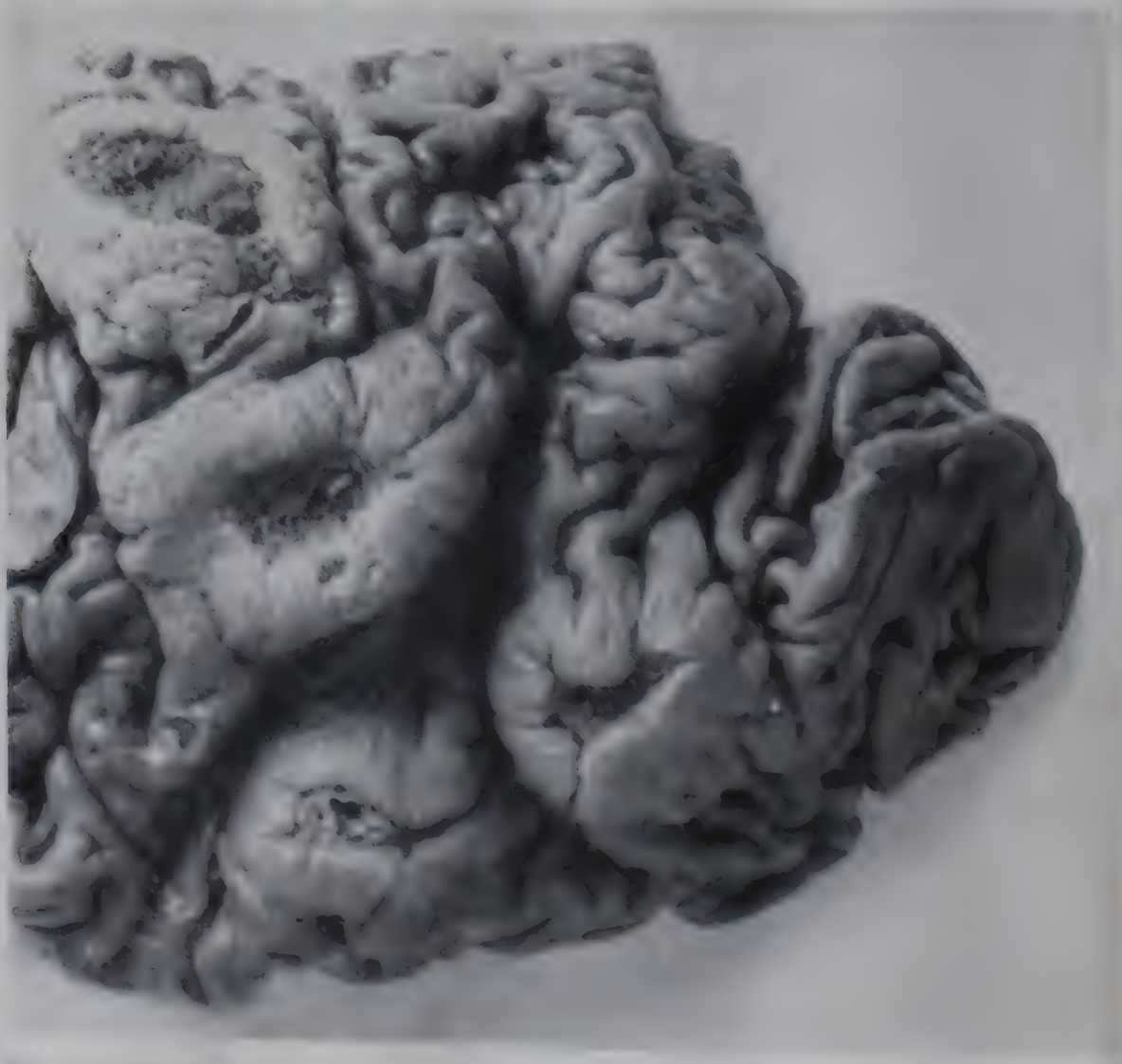


FIG. 14. Multiple chronic ulcers in the stomach of a sea lion. (Courtesy, Dr. A. V. Kelly, Biological Research Institute, San Diego, California.)



FIG. 15. Healed gastric ulcer in the stomach of a sea lion. (Courtesy, Dr. A.V. Kelly, Biological Research Institute, San Diego, California.)

tated. The stones available on the Lower California group of islands are sharp black lava; these sharp stones injure the mucosa, providing a ready portal of entry for the gastric nematodes which feed on or in the newly formed granulation tissue, prevent healing, and cause proliferation of connective tissue. Perforation of the ulcer may occur, and study of the lesion indicates that the perforation is due to acute activity at the site of a chronic lesion. Seals secrete acid in response to histamine much like the human, but free acid has not been found in their fasting gastric residuum (24).

The failure to find chronic gastric ulcer in seals residing in areas where sharp stones are not available and nematode infestation is not conspicuous shows that in the absence of these etiologic factors seals are not prone to develop ulcer. This experiment in nature demonstrates that mechanical trauma plus irritation of the edges of the ulcer are significant etiologic factors of chronic ulcer (see p. 158).

We have observed two specimens of chronic gastric ulcer infested with nematodes in the turtle.

Calves

Further evidence for the etiologic role of *trauma ab ingestis* is found in the occurrence of stomach lesions in weanling calves. The frequency of these lesions has been reported by one observer (26) as given in Table 2. These ulcers are attributed to the fact that calves are weaned before they have developed the ruminating function. Thus the partly

Table 2

INCIDENCE OF GASTRIC LESIONS IN CALVES*

Age	*No. of Calves Examined*	*Incidence of Gastritis, Erosions, and Ulcers*	*Incidence of Chronic Ulcer*	*Incidence of Scars*
4–6 wk.	320	80.6%	..	
8 "	160	95%	2.5%	
10 "	160	95.6%	5.0%	
12–14 "	200	98%	2.0% (healing)	7.5%
6 mo.–2 yr.	200	0	0	Frequent

* Prepared from the data of Bongert (26).

masticated fodder passes almost directly into the glandular part of the stomach. In connection with the rate of healing (Chapter 5), it is interesting that, in these calves, the healing apparently begins some time after the tenth week and generally is complete between the twelfth and fourteenth weeks. This indicates a healing time of approximately three weeks, which is in good agreement with the figures obtained from experimental and clinical observations.

Miscellaneous

Most textbooks on veterinary medicine do not mention peptic ulcer. Hutyra and Marek (22), in their comprehensive treatise on the pathology of domestic animals, state that ulcer of the stomach is rare in these animals. They cite references to their rare occurrence in adult cattle, in dogs, swine, and horses. A case of the perforation of a gastric ulcer in a horse was the subject of a paper by Schlotthauer (21) and an epizootic of perforating gastric ulcer in ranch foxes, presumably infectious in origin, was reported by Schillinger (20).

Fox (23), in his monograph on "Diseases in Captive Wild Animals and Birds," reports that chronic gastric ulcer is not common. He states: "True peptic ulcers have been found in Primates, 4; Carnivora, 5; Pinnipedia, 2; Insectivora, Ungulata and Hyraces each 1." "Six of the 13 instances occurred on the greater curvature, the remainder on the lesser. Ten ulcers were in the pyloric division, the other four being scattered."

Summary

The occurrence of *chronic or subacute gastric or duodenal ulcer* in the healthy dog, cat, rat, guinea pig, rabbit, pig, steer, sheep, and monkey is very rare. Seals, when they swallow sharp stones and are exposed to gastric nematode infestation, develop chronic gastric ulcer spontaneously in the majority of instances. Table 3 summarizes these facts.

The fact that common laboratory animals do not frequently develop chronic ulcers of the stomach and duodenum spontaneously is advantageous in that it accords etiologic significance to a procedure which may cause an acute or a chronic ulcer and it permits the analysis of the relative etiologic significance of individual factors. However, when animals are used the question of species differences arises; the failure of peptic ulcer to occur spontaneously in animals lower than man as frequently as they do in man (except in the seal where the etiologic factors are quite clear), is a species difference. The fact that they do occur renders it possible to use the subhuman species for etiologic and therapeutic studies with the same caution that must always attend the application of the results of animal experimentation to man.

Table 3

Animals	*Number Reported*	*Incidence of Ulcer*	*Observers*	
Dog	271	0	Turck	(1906)
Dog and cat	200	0	Mann	(1916)
Dog (healthy)	1,000	0	Ivy	(1919)
Dog	100	0	Battaglia	(1927)
Dog	1,000	0.8%	Overgaard	(1934)
Dog	150	0	Keller	(1936)
Dog	55	0	Volini	(1938)
Rat	200	8%	Singer	(1913)
Rat	1,189	0	McCarrison	(1931)
Rat	75	0	Howes	(1936)
Guinea pig	1,000	0	Smith	(1933)
Monkey	50	0	Hoff	(1935)
Monkey	300	0	Watts	(1935)
Rabbit	100	0	Beazell	(1936)
Swine (ill)	754	2.4%	Kernkamp	(1945)
Swine	1,000	0	Ivy	(1926–30)
Seals	46	100%	Schroeder and Wegeforth	(1935)

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OUTLINE OF CHAPTER 4

Resistance of Stomach to Digestion

I. Introduction
II. Theory of the "Living Principle"
III. Theory of the Protective Action of the Epithelium
  A. the proof that pepsin is not absorbed by the uninjured cell
  B. the proof that acid is a factor causing injury
  C. sublethal damage of cells increases susceptibility to digestion
  D. the gradient of susceptibility to injury by acid or acid-pepsin in the gastrointestinal tract
  E. is the surface epithelium of the stomach continuously renewed?
IV. Theory of the Protective Action of Mucus
  A. diffusion of acid and pepsin through mucus
  B. mucus inhibits peptic digestion
  C. mucus is resistant to peptic digestion
  D. mucus possesses some neutralizing and buffering capacity
  E. mucus is rendered more viscous by acid and less so by alkalies
  F. mucus coats the epithelium of the stomach more or less continuously
  G. secretions of the intestinal mucosa
V. Theory of Protection by the Blood Supply
  A. theory of protection by the alkalinity of the blood
    1. The Deeper Layers of the Stomach Are Not Digested When a Patch of Mucosa Is Removed
    2. The Spleen and Kidney When Implanted into the Stomach Are Digested
    3. The Role of the Blood Is Not So Important in Neutralizing Acid as It Is in Preserving the Life of Cells

B. THEORY OF PROTECTION BY THE NUTRITIVE FUNCTION OF THE BLOOD
1. The Localized Necrosis of Cells Results in the Formation of an Erosion or an Acute Ulcer
2. Local Injury to Cells May Release Histamine Which May Cause Local Arteriolar Spasm and Decreased Resistance to Digestion

VI. THEORY OF THE RESORPTION INTO THE BLOOD OF DIGESTIVE FERMENTS

VII. THEORY OF THE "BIOCHEMICAL RESISTANCE" OF THE LIVING CELL
A. CERTAIN ORGANISMS LIVE IN THE DIGESTIVE JUICES
B. ALL LIVING MATTER SHOWS SOME RESISTANCE TO DIGESTION
C. SENSITIVITY OF CELLS TO ACIDS AND ALKALIES
D. LIMITS OF TOLERANCE OF CELLS TO ACIDITY AND ALKALINITY
E. ONLY A SMALL PORTION OF THE CELL IS EXPOSED TO THE DIGESTIVE JUICES

VIII. THEORY OF PROTECTION BY ANTIFERMENTS
A. THE ANTIPEPTIC ACTIVITY OF PLASMA AND TISSUES IS NOT DUE TO A SPECIFIC ANTIPEPSIN IN THE IMMUNOLOGIC SENSE
B. NONSPECIFIC INHIBITORS OF PEPTIC AND TRYPTIC ACTIVITY

IX. A CONSIDERATION OF THE RESISTANCE OF TISSUES TO PANCREATIC JUICE AND ITS ENZYMES
A. THE PANCREAS DIGESTS ITSELF UNDER CERTAIN CONDITIONS
B. THE INTESTINE WILL DIGEST ITSELF POSTMORTEM AND WHEN INJURED
C. THE DRAINAGE OF PANCREATIC JUICE INTO THE STOMACH AND COLON DOES NOT CAUSE DIGESTION OF THE MUCOSA, WHEREAS ITS PRESENCE IN THE GALLBLADDER DOES
D. THERE IS NO EVIDENCE SHOWING THAT THE PANCREATIC ENZYMES ARE ABSORBED FROM THE LUMEN OF THE BOWEL
E. OTHER ENZYMES

X. ADAPTATION OF THE SURFACE EPITHELIUM AND THE GLAND TUBULES TO THE SECRETIONS AND SECRETORY MECHANISMS IN RELATION TO THE NATURE OF THE RESISTANCE OF THE MUCOSA TO AUTODIGESTION
A. STOMACH
B. INTESTINE
C. ADAPTATIONS OF THE GASTRIC GLAND TO HCL-PEPSIN

D. ADAPTATIONS OF THE PANCREATIC CELL AND TUBULAR EPITHELIUM TO ITS SECRETION

XI. SUMMARY

A. STOMACH

B. INTESTINE

C. PANCREAS

XII. CONCLUSIONS

CHAPTER 4

Resistance of Stomach to Digestion

Introduction

"Why does not the stomach digest itself during life?" is a question intimately related to the etiology of peptic ulcer. Or, in a broader sense, how can we account for the resistance of living tissues to digestion by their own digestive juices? This question arose as a natural consequence to early physiologists, once the study of the digestive processes made it apparent that the ingested food was attacked and liquefied by the digestive juices. Many of the pioneers in the study of digestion devised ingenious experiments in an attempt to solve the problem.

The various theories which have been proposed will be presented in their historical sequence. It will be observed that any one of the theories or mechanisms proposed is inadequate to account for the observed facts. In the presentation of the theories some modern observations which are pertinent to the relative adequacy or inadequacy of each theory will be considered. The chief purposes of this chapter are (a) to provide certain items of basic information necessary for the interpretation of experimental findings to be presented later, (b) to indicate that several mechanisms operate to prevent autodigestion, and (c) to point out that the gastrointestinal mucosa is digested under certain abnormal conditions.

Theory of the "Living Principle"

John Hunter (1), in a report to the Royal Society in 1772, attempted the first explanation of the resistance of living tissue to gastric digestion. His theory is embodied in the following statement:

> Animals, or parts of animals, possessed of the living principle, when taken into the stomach, are not the least affected by the powers of that viscus, so long as the animal principle remains; thence it is that we find animals of various kinds living in the stomach, or even hatched and bred there; but the moment that any of those lose the living principle, they become subject to the digestive powers of the stomach. If it were possible for a man's hand, for example, to be introduced into the stomach of a living animal, and kept there for some considerable time, it would be found, that the dissolvent powers of the stomach could have no effect upon it; but if the same hand were separated from the body, and introduced into the same stomach, we should then find that the stomach would immediately act upon it.

This vague concept remained the only theory available on the subject until 1856, when the experiments of Claude Bernard and of Pavy demonstrated conclusively that "parts of animals, possessed of the living principle, when taken into the stomach" are very definitely "affected by the powers of that viscus." And it was with the work of these investigators that the more definitive theories of the resistance of the living stomach to digestion began to take form.

Theory of the Protective Action of the Epithelium

Bernard (2), in the well-known experiment in which he placed the leg of a living frog inside a dog's stomach, disproved the theory of Hunter by showing that within three-quarters of an hour considerable digestion of the frog's leg had taken place. However, no digestion of the author's own finger occurred when he kept it in the stomach for a long time, and it was partially for this reason that he postulated the presence of a continuously renewed, protective epithelium which prevents digestion. To quote Bernard,

> If the gastric juice does not digest the walls of the living stomach, it is because during life it is impossible for pepsin to be absorbed. The presence of the epithelium on mucosae in general, especially on the gastric mucosa, places a complete obstacle to the absorption of a certain number of organic materials; the ferments destined to act on aliments are thus arrested. . . The epithelium of the gastric mucosa, especially the glutinous mucus which covers the inner wall of this viscus and which is seen very well when one opens the living animal, thus incloses the gastric juice as in a vase as impermeable as though it were made of porcelain.

Bernard maintained, in essence, that the stomach does not digest itself because pepsin is not absorbed by the cells, and the mucus-secreting cells of the surface epithelium are continuously renewed. Bernard failed to consider adequately the acid factor and to prove that pepsin is not absorbed.

The Proof That Pepsin Is Not Absorbed by the Uninjured Cell

Bernard's suggestion that pepsin is not absorbed by living cells was challenged by several investigators who found in human urine a proteolytic enzyme which acts in the presence of hydrochloric acid (3–8). This was considered to constitute evidence that pepsin is absorbed from the alimentary canal into the blood and is then excreted in the urine. The gastric origin of this pepsin-like protease in the urine is well established (13); however, it probably is secreted directly into the blood by the chief cells of the fundic glands and probably is not absorbed from the gastric lumen.

Theoretically, gastric pepsin would be irreversibly inactivated at blood pH. If, however, the enzyme were absorbed in the form of pepsinogen, then it could withstand the pH of blood, and, if excreted into the urine, would be transformed into active pepsin upon acidification. Thus, in order for active pepsin to appear in the urine, pepsinogen must be discharged directly from the chief cells into the blood stream, or it must be resorbed from the gland tubule or the gastric mucosal surface before it has been transformed into pepsin. The former process, discharge of enzymes from the secretory cell directly into the blood, is known to occur in the case of the salivary glands and the pancreas. Under normal conditions small quantities, and under certain pathologic conditions considerably larger amounts, of the enzymes from these glands gain entrance to the blood. It is reasonable to assume that a similar process could occur in the gastric glands. This, then, would represent not an absorption of enzymes but a type of "endocrine" secretion by exocrine glands of enzymes not inactivated by the alkalinity of the blood.

The presence in normal human urine of a protease which is active in an acid medium has been confirmed recently, using refined methods for enzyme estimation (10, 11). A further point of evidence in favor of the view that the urinary protease is gastric pepsin is the recent demonstration that the content of this protease is significantly reduced in pernicious anemia patients (12), and the confirmation of earlier experimental work showing that the protease disappears from the urine after total gastrectomy in cats (13).

Northrop (14) has performed experiments which show that pepsin and trypsin are not absorbed by uninjured living tissue. When earthworms, yeast, and amebae were placed in a solution of pepsin or trypsin, no quantity of enzyme was absorbed. When the cells were killed by heat, strong HCl, or alcohol, the enzyme was rapidly removed from the solution and concentrated in the cell. When the enzyme solution was injected into a cell (*Ameba*), disintegration of the cell occurred. It was concluded that these enzymes do not enter the uninjured living cell due to the properties of its membrane.

Thus, this evidence shows that pepsin is not absorbed by the uninjured living cell.

The Proof That Acid Is a Factor Causing Injury

Bernard's view that the acid of gastric juice was lactic rather than hydrochloric acid may account for his failure to recognize the significance of the acid factor. However, he could have exposed the legs of frogs to neutralized and non-neutralized solutions of gastric juice. Nor did this possibility occur to Pavy (15–18), who extended Bernard's experiment on

the frog to include the ear of the rabbit. He used the rabbit because he believed that Bernard's work on the frog did not entirely rule out Hunter's "living principle," "since the latter may be supposed not to exist in the frog—a reptilian and cold blooded animal." The fact that the living rabbit's ear was digested when introduced into a dog's stomach through a gastric fistula caused him at first to accept Bernard's theory. Later he proposed a theory of his own.

Ewald (19) was unable to accept Bernard's hypothesis because he found that "the well-shaved foot of a living dog, kept for six hours at room temperature in a very active mixture of glycerine-stomach extract plus HCl, was not attacked, even though the hind extremities of the dog were paralyzed as a result of cord section." The implication of this observation is, of course, erroneous, because it is well known that the skin about a gastric fistula is digested unless protected from the more or less continuous contact with gastric juice.

A more critical investigation of the frog experiments of Bernard and Pavy was made by Frenzel (20) who considered their work incomplete because they did not investigate the separate effects of acid and of pepsin. To accomplish this, the author suspended a frog so that one leg was immersed in 0.2 per cent HCl, the other leg in pepsin-HCl (0.2 per cent) solution. After incubation for one and one-half hours, the leg exposed to the pepsin-HCl was digested down to the bone, and the solution gave a strongly positive peptone reaction. The other leg showed no significant changes in a corresponding length of time, even when the skin was removed and the muscle exposed; the same result was obtained with neutral pepsin. Frenzel suggested that the digestion was not really one of living tissue, but that the tissue was first killed and then digested; neither the acid nor the pepsin alone possesses the power to kill the tissue—it is only in combination that they are effective. Therefore, the cells of the living stomach, whether epithelial or otherwise, should theoretically be digested by the gastric secretion. The reason why this does not occur, according to Frenzel, is not explained adequately by Bernard's theory. He was not yet prepared, however, to offer another explanation of the phenomenon. Frenzel's experiments were confirmed by Warren (21).

Matthes (22) agreed with Frenzel that Claude Bernard's experiment failed to explain why the stomach was not digested by gastric juice, but he did not agree that it required the combination of acid plus pepsin to kill the tissue preparatory to digestion. According to Matthes, the acid of the gastric juice was primarily responsible for the destruction of living tissue. His explanation for the process was as follows: frog skin does not withstand acid, and is therefore corroded by it; the eschar thus formed acts as a protective barrier against the further action of the acid. In the

presence of pepsin, this dead eschar is dissolved and the acid acts anew on the underlying tissues. For experimental proof of this view, the author substituted an innocuous acid which does not attack the skin; for example, combinations of hippuric acid with pepsin had no effect on the frog's leg, although the solution digested egg white. (When Frenzel and Matthes did their work the importance of the pH of the solution for the action of pepsin was not known.) Fermi (23) observed no digestion of the extremities of frogs and tritons by the gastric juice of dogs and frogs unless the experiment was conducted at 38° C., or HCl in a concentration of 0.06 per cent was added. His other observations, indicating that a cell (yeast) had to be injured before it was digested, conform with those of Northrop cited above.

A rather novel approach to the problem was presented in 1907 by Neumann (24), who considered that the use of neither the frog's leg nor the rabbit's ear was strictly applicable to the question of why the stomach is not digested by its own secretions. In one of his experiments, therefore, he caused the frog's stomach to become everted through its mouth; he then snipped off a piece of the mucosa and muscularis (and accidentally, a piece of the serosa), and returned the stomach to its original position. When the frog was sacrificed eight days later, the site of the defect was occupied by a well-developed scar; this indicated that the frog's stomach resisted its own secretion. In further experiments, Neumann introduced the leg of a small living frog into the stomach of a larger one, and found that there was no digestion of the donor's leg in a period of time up to 23 hours. The author considered these findings contradictory to the classic observation of Bernard, and concluded that the vital body tissues are immune to the gastric secretion of the same or related species, whereas they are liable to digestion by foreign peptic secretion. However, Dragstedt and Vaughn (25) showed that a frog's leg *is* digested in a 0.4 per cent HCl extract of frog's gastric mucosa.

Within recent years, Bernard's experiment has been confirmed and somewhat extended. Dragstedt (26) found that pure gastric juice of normal pepsin concentration, but with the free acidity reduced to 0.109 per cent or less, had no digestant action on the frog's leg, whereas juice having a concentration of free acid of 0.18 per cent or more had a very marked effect, almost irrespective of the concentration of pepsin; that is, a concentration of HCl somewhere between 0.1 and 0.15 per cent was shown to be the critical level at or above which living tissue was digested. Warren (21) in 1887 reported that he obtained digestion of the frog's leg with acid-pepsin solutions in which the concentration of acid was as low as 0.05 per cent. Necheles and his co-workers (27, 28) demonstrated that the digestion of a frog's leg immersed in 2 per cent pepsin–0.1N HCl solution at 38° C. was accelerated by anesthesia, section of the sciatic nerve,

and exposure of a large surface to the digestive juice. They accept Matthes' interpretation of the observed facts; namely, acid corrosion or injury followed by peptic digestion.

In the foregoing discussion, Bernard emphasized pepsin as the potentially injurious factor in gastric juice and Matthes emphasized acid. Of course, pepsin in the absence of acid is impotent. When the "peptic activity of gastric juice" is referred to, the expression implies the action of HCl-pepsin, and not acid or pepsin alone. Pepsin is never absent from gastric juice which contains acid.

It is worthy of emphasis that acid in sufficient concentration will injure cell membranes and cells in the absence of pepsin. The concentration required varies with the cell, as will be indicated subsequently (p. 75). Acid denatures protein; denatured protein is much more susceptible to enzymatic digestion than native protein.

Sublethal Damage of Cells Increases Susceptibility to Digestion

Bolton (29) performed a significant experiment, the results of which showed that a sublethal injury of the cells of the gastric mucosa decreased their resistance to digestion by gastric juice. He produced a "gastrotoxic serum," for example, by injecting a normal saline extract of the gastric mucosa of the guinea pig into a rabbit. The rabbit serum, when injected into a guinea pig, produced hemorrhagic erosions and acute ulcers. However, if he neutralized the gastric contents with 1 per cent sodium bicarbonate solution before and after the injection, no such lesions occurred. He found further that gastric mucosa which was not injured by 0.5 per cent acetic acid or 0.2 per cent HCl was injured by such solutions after injecting "gastrotoxic serum." In the experiments in which he prevented lesions from resulting by neutralizing the gastric contents, the cells were found to appear normal histologically. The serum thus rendered the cells susceptible to digestion without actually killing them. So, actual death of cells is not necessary to render them abnormally susceptible to digestion by gastric juice.

The Gradient of Susceptibility to Injury by Acid or Acid-Pepsin in the Gastrointestinal Tract

As indicated above, Matthes (22) was impressed by the fact that the skin was more readily injured by gastric juice than was the mucosa of the stomach. He concluded that the resistance of living tissues to digestion represents a specific adaptation of the cells to their environmental conditions.

He performed an important experiment which showed that the stomach was more resistant to acid than was the jejunum. He found that when

hydrochloric acid, in a physiologic concentration readily withstood by the stomach, was perfused through a loop of jejunum in the dog, necrosis of the superficial cells occurred. This was confirmed by Langenskiold (30) and by the method of implanting strips of duodenum and jejunum into the stomach (31, 32). These and similar but more quantitative experiments by others will be discussed later (Chapter 10).

Is the Surface Epithelium of the Stomach Continuously Renewed?

Bechamp (33) believed that the stomach must inevitably digest itself constantly, because of the activated peptic secretion acting at a physiologic temperature on a protein substance. But, according to him, it is not apparent that the mucosa is being destroyed because there is a constant formation of new cells to take the place of those disappearing through usage. That is, in the living stomach, production of new epithelial cells is equal to consumption.

It is well known that all epithelial surfaces are subject to wear and tear and renewal. However, the rate at which the surface epithelial cells of the stomach or intestine are normally renewed has not been studied. Hollander (34) has found that when the gastric mucosa is irritated, ranks of epithelial or mucous cells may be found in the mucus. The rate at which the superficial cells are regenerated is remarkable. Grant (35) reports that when a superficial erosion is produced by treating the mucosa with 50 per cent alcohol or 1 per cent acetic acid, distances as great as 0.2 to 0.4 mm. per hour are covered by the migrating epithelial cells (Fig. 16). This is more rapid than regeneration of the skin (36). It is believed that the cells on the surface are renewed by migration of epithelial cells from the adjacent gland tubules. This repair of superficial damage by migration of cells without mitotic activity is to be contrasted with the repair process in a true ulcer.

Theory of the Protective Action of Mucus

Closely allied with Bernard's theory of the protective action of the gastric epithelium is the theory of the protective action of mucus-secreting epithelium. In fact, Bernard included the protective action of gastric mucus in his theory, though he performed no experiments on the point (p. 57).

In 1860, Harley (37) recognized that the living tissue of a warm-blooded animal was susceptible to digestion by the animal's own gastric juice. "If . . . some gastric juice be taken from an animal's stomach and introduced under the skin of its back or belly, in a few hours the fluid will be found to have digested its way out, and left a hateful looking wound."

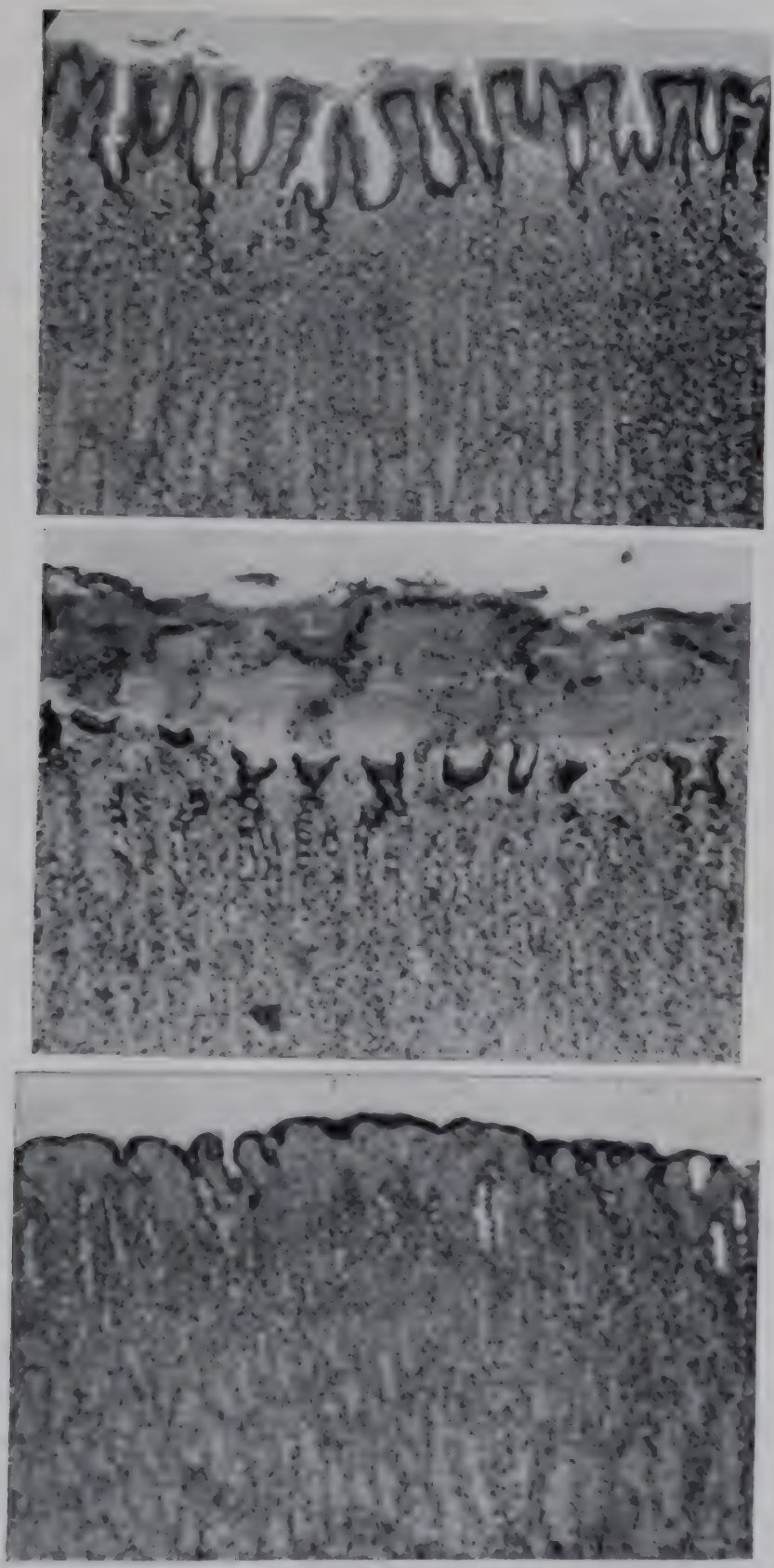


FIG. 16. Showing replacement of surface epithelium of the gastric mucosa of the cat after injury produced by the application of 60 per cent alcohol. (*Top*) Control mucosa; (*center*) 12 minutes after removal of alcohol; (*bottom*) showing that the epithelium has been replaced 5.75 hours after removal of alcohol. (Courtesy, Rhoda Grant, *Anat. Rec.*, **91**:175.)

He disagreed with the view of Bernard that the resistance of the epithelial cells explained the nondigestion of the gastric mucosa. He believed that the mucous secretion of these cells was the important factor, because he found experimentally that "if a stomach be divided into two parts and from one of the halves the mucus be carefully removed . . . while the other half is left intact, it will be found, on making each into a sort of bag, and filling it with pure gastric juice, that a few hours' exposure to an elevated temperature will suffice for the solution of the half from which the mucus was removed, whereas the other . . . will remain unacted upon."

Schiff (38) in 1867 also performed experiments which demonstrated the protective action of mucus. He found that when pieces of excised portions of the stomach were exposed to peptic digestion, in vitro or in vivo, the surface epithelium, which contains mucin, was more slowly digested than the muscularis. This observation is easily confirmed. He also demonstrated that a layer of mucus secreted by the stomach serves as a barrier against digestion. In a dog, he introduced two rigid tubes through a gastric fistula into the empty stomach. One tube was used for the introduction of nourishment to stimulate gastric secretion; the other was placed in contact with the mucosa. When, after two hours, the end of the second tube was covered with a layer of mucus, he introduced into this tube a piece of meat or of cooked egg white so that it came into contact with the mucus. After ten hours the egg white and meat were not digested, though acid in reaction; Schiff concluded that the mucus had permitted acid, but not pepsin, to diffuse through.

Diffusion of Acid and Pepsin through Mucus

Schiff's observations in both instances were confirmed by our (39) dialysis experiments with various types of kinetometers, using mucus collected freshly from a pouch of the pyloric antrum. It was found that the diffusion of HCl and pepsin through mucus occurred after 12 to 72 hours, depending upon (a) the viscosity of the mucus, (b) the thickness of the layer of mucus, (c) the acidity of the gastric juice used, and (d) the character of the fluid against which the gastric juice was dialyzed. A layer of very viscid mucus 1 mm. thick delayed diffusion of HCl in gastric juice (0.36 per cent acid) for from 12 to 18 hours. Pepsin was detected in the dialysate 3 or 4 hours after the acid; however, the method for the detection of pepsin was less sensitive than that for acid. Bucher (40) also studied the rate of the diffusion of acid and pepsin through gastric mucus; he used silk to hold the mucus in place, whereas we (38) used tissue paper (lens paper) or cotton gauze, except when the mucus was so viscous that nothing was

required to hold it in place. Bucher found that acid and pepsin diffused rapidly at first, decreasing after one hour, and then increased again after 2 or 3 hours.

Mucus Inhibits Peptic Digestion

Klug (41) found that gastric mucus and mucus from other sources, such as bile, pseudomucinous ovarian cysts, and saliva, inhibit peptic and tryptic digestion, a property that was not destroyed by boiling. This is also true of plant gums and mucilages (42, 43) which in most instances pass through the alimentary tract undigested. The protective effect of gastric mucus against peptic digestion has also been demonstrated by using Bernard's frog method (44).

Several investigators, using more modern methods, have confirmed Klug's observation that mucus inhibits peptic digestion (45–49). (See Fig. 17.) The "antipeptic" action of mucus probably is due to adsorption (47), augmented by the inhibitory effect of products of partial digestion of the mucus (45, 49).

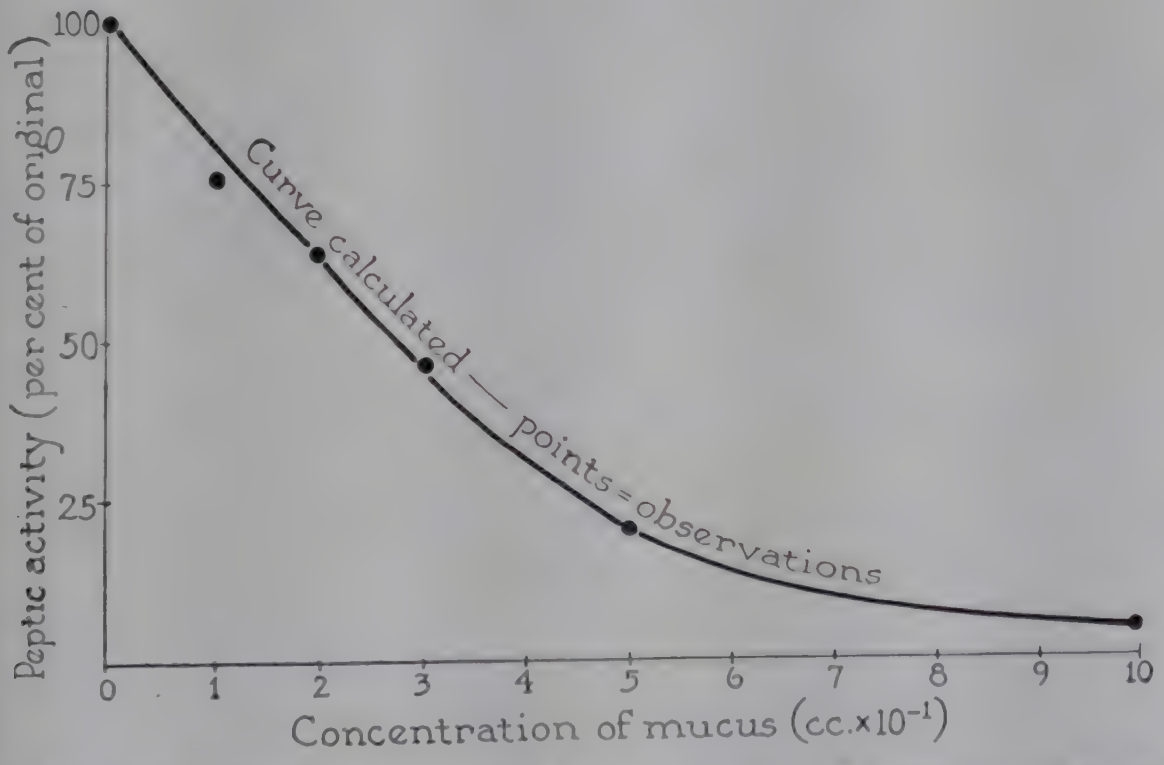


Fig. 17. Showing the relation of the concentration of pyloric mucus to the degree of inhibition of the action of pepsin. Increasing amounts of pyloric pouch mucus were added to a digestion mixture containing 1 mg. of crystalline pepsin. The volume, concentration of pepsin, concentration of hemoglobin substrate, and pH of the digestion mixture were kept constant; the concentration of mucus was varied. The solid curve was calculated from the law of mass action; the points were experimentally observed.

Mucus Is Resistant to Peptic Digestion

Gastric mucus is relatively resistant to peptic digestion, which might be surmised from Schiff's observation that the epithelium of the stomach is more slowly digested than muscle. Sometimes it is digested in less than 24 hours and sometimes it is not digested in several days (50–53). In our experience, the rate depends on the viscosity of the mucus. Anderson and Farmer (54) prepared a gastric mucin which was entirely resistant to peptic digestion. Bucher (40) reports that the layer of gastric mucus starts to digest in from 2 to 4 hours and must be replaced by secretion, a report that requires confirmation. The mucus secreted may be renewed frequently, but very probably is removed by the movements of the stomach rather than by digestion.

Mucus Possesses Some Neutralizing and Buffering Capacity

Gastric mucus possesses some neutralizing and buffering capacity for acid; the reports on the extent of the buffering capacity vary, due to the variations in the preparations of gastric mucus used (55–59). The pH of the mucus secreted by the pyloric mucosa ranges from 7.0 to 7.5 (60); mucus collected from the acid-secreting mucosa may be slightly acid in reaction, as might be expected. One gram of mucus collected from the human stomach by tube, according to Mahlo (55), will combine with 16 to 18 cc. of 0.1N HCl. This subject has been discussed completely by Babkin (61). It is probable that most of the buffering capacity of mucoid secretions is due to dialyzable buffer salts. The mucopolysaccharides themselves have little buffer capacity.

Mucus Is Rendered More Viscous by Acid and Less So by Alkalies

Gastric mucus becomes more viscous as the acidity is increased (40, 55, 62, 63). This may be interpreted as indicating that as the acidity of the gastric contents increases, the mucus becomes a more effective barrier. Bucher (40) pointed out that alkalies, which decrease the viscosity of mucus quite decidedly, counteract the protective property of mucus. He gave 5 Gm. of $NaHCO_3$ in powder form daily to dogs and observed small hemorrhagic erosions of the mucosa of the greater curvature in one case; since he used a tube, this observation is open to criticism, for we know that considerably more $NaHCO_3$ (20 Gm. daily) can be given to dogs without obtaining erosions when a stomach tube is not used. However, it is certain that an alkaline reaction in the stomach decreases the viscosity of the mucus, rendering it quite thin; on the other hand, excess acid can coagu-

late and "clump" the mucus and, thus, decrease its capacity to cover the mucosa with a more or less continuous layer.

Mucus Coats the Epithelium of the Stomach More or Less Continuously

It is well established that mucus is secreted more or less continuously in the stomach, duodenum, and jejunum (also the colon) (60, 61). Bucher (40), who used the Regaud fixative and serial sections, maintains that a continuous layer of mucus varying in thickness from 0.5 to 1.5 mm. is to be found covering the entire surface of the stomach; the layer is thinnest along the lesser curvature and in the cardiac region. He used specimens of human stomach excised at operation. We can confirm this report for the pyloric mucosa of the empty stomach of the dog, and it is generally true of the entire empty stomach of the pig. We cannot confirm the report for the acid-secreting portion of the gastric mucosa of the dog, though we have not used the Regaud fixative. According to Bucher, the gastric juice gains entrance to the lumen of the stomach by passing through the continuous layer of the mucous film, by coagulating and thus loosening the mucous gel network. The secretory pressure of gastric juice must also be involved, if the film is actually continuous.

Thus, gastric mucus is believed to protect the stomach by (a) its presence in the surface epithelial cells, (b) its resistance to peptic digestion, (c) its inhibition of peptic activity, (d) its capacity to neutralize and buffer acid, (e) its tendency to become more viscous with an increase in acidity, and (f) its tendency to cover the gastric mucosa by a more or less continuous film.

Secretions of the Intestinal Mucosa

The older investigators were primarily interested in gastric ulcer or in explaining why the stomach does not digest itself; today, duodenal ulcer is more frequent than gastric ulcer, and a new disease—jejunal ulcer—has been produced surgically. Hence, the theory of the protective action of mucus must be extended to include the secretions of the upper intestine.

The upper intestine produces three secretions: (a) mucus, (b) succus entericus or intestinal juice, and (c) Brunner's gland juice.

The *goblet cells*, which secrete mucus, are interspersed among the epithelial cells which cover the villi. The cells of the crypts of Lieberkühn, which are found at the base of the villi, probably secrete the intestinal juice, though it is not certain whether these cells secrete and the cells of the villi absorb, or whether both types of cells do both. The intestinal juice in the dog is generally slightly alkaline, pH 6.3 to 8.0; its neutralizing value is equivalent to a 0.2 to 0.67 per cent Na_2CO_3 solution. The volume

of the secretion in response to mechanical and chemical stimulation varies widely from 10 to 115 cc. per hour for a loop of jejunum or upper ileum from 25 to 50 cm. long.

The Brunner's glands in the dog are confined chiefly to the first one or two inches of the duodenum, though in man they extend to the upper jejunum (Chapter 1), where they are relatively sparse. The secretion is mucoid in nature, but its content of mucinous material varies in different species. It is definitely alkaline in reaction, having a pH varying from 8.2 to 9.0; the neutralizing power of 1 cc. of Brunner's gland secretion of the cat, dog, and pig is equivalent to that of 0.25 to 0.5 cc. of 0.1N Na_2CO_3. The secretion of these glands has not been studied in man, but histologically the glands of man resemble quite closely those of the pig (64, 65). Florey and Harding (64) have suggested that duodenal ulcer may be due to a decrease in the secretion of the glands of Brunner, a suggestion which has not received the experimental study it merits.

The epithelium of the stomach is more resistant to HCl-pepsin than that of the duodenum and the jejunum (see p. 221). This difference undoubtedly is due chiefly to the continuous layer of mucus-secreting epithelium possessed by the stomach and not by the intestine. The difference between the duodenum and jejunum is best accounted for by the scarcity of Brunner's glands in the latter, or the greater secretory activity of the mucosa of the duodenum. Nevertheless, these factors are not specific, and are not the only factors concerned in preventing autodigestion. For example, it will be shown later that intestinal mucosa implanted into the wall of the stomach is not digested. Even before these observations had been made, Pavy had removed a patch of mucosa from the stomach and had observed the defect to heal while the animal was digesting its usual diet; this proved that the surface epithelium is not the sole factor in preventing autodigestion.

Theory of Protection by the Blood Supply

Theory of Protection by the Alkalinity of the Blood

Although this hypothesis is frequently attributed to Pavy, and is referred to in the German literature as the theory of Virchow-Pavy, it appears that Virchow conceived the idea about 10 years before Pavy, as indicated by the following statement (66) by the German pathologist in 1853: "As soon as the customary circulation to the stomach is interrupted, then also are lacking the possibilities of the usual neutralization of the inflowing acid by the alkalies of the blood, and corrosion will follow." It was not then known that when the acid-secreting cells are deprived of an active circulation, acid formation promptly ceases. In such a case, if

an ulcer, or autodigestion, occurs, it must be due to the acid-pepsin secreted prior to the onset of the circulatory embarrassment.

THE DEEPER LAYERS OF THE STOMACH ARE NOT DIGESTED WHEN A PATCH OF MUCOSA IS REMOVED. In 1863, Pavy (16) found it necessary to reject Bernard's theory of the protective action of the surface epithelium as the sole explanation for the resistance of the stomach to autodigestion. He made the important discovery that in the dog's stomach "a considerable patch of mucous membrane may be removed, and food will afterwards be digested without the slightest sign of attack being made on the deeper coats of the organ." Therefore, he expressed the opinion that the resistance of the stomach was due to the alkalinity of the blood flowing through the mucosa, opposing the action of the acid. The advancement of this view made it necessary for the author to explain why the frog's leg and rabbit's ear, both with intact circulation, were attacked by the gastric juice; this he did by stating that a quantitative difference existed between the blood supply to the stomach and that to the ear or leg, and that if the circulation to the stomach is correspondingly reduced by ligation of its vessels, the stomach is digested. In later experiments (17, 18) he enlarged the theory by pointing out that two opposing forces are concerned in autodigestion of the living stomach: (a) the acidity of the juice, and (b) the alkalinity of the blood. The fate of the gastric mucosa depends on which of these forces is the stronger.

Pavy's observation that the removal of a patch of mucosa is followed by healing in from several days to two or three weeks has been confirmed on various animals; however, autodigestion of the stomach does not result from ligation of almost all the arteries along the lesser and greater curvatures, a procedure which temporarily decreases markedly the gastric secretion (67–75). Thus, the significance of Pavy's work is not that it answers the question why the stomach does not digest itself, but rather that it raises the equally important questions why does the acid-pepsin not digest the exposed cells in an area where the gastric epithelium has been removed, or why does the acute ulcer so produced heal rapidly?

The Virchow-Pavy theory was challenged by Samelson (76), who, not knowing of the remarkable acid-buffering capacity of the blood, injected acid intravenously to counteract its alkalinity and failed to produce self-digestion of the stomach.

THE SPLEEN AND KIDNEY WHEN IMPLANTED INTO THE STOMACH ARE DIGESTED. Bocci (77) introduced a new experiment in 1880 to test the Virchow-Pavy theory. He implanted the spleen, a well-vascularized organ, into the stomach; he observed that the spleen was digested, and concluded that the theory of Virchow and Pavy was erroneous. Further organ-implantation experiments have been performed, as will be discussed in Chapter 5.

THE ROLE OF BLOOD IS NOT SO IMPORTANT IN NEUTRALIZING ACID AS IT IS IN PRESERVING THE LIFE OF CELLS. Warren (21) could not accept the Virchow-Pavy view, because he found that local digestion of living muscle may be produced by pepsin in combination with an acid of such weak concentration that the entire amount of acid employed is less than that which the blood might be expected to neutralize. Similarly, Ruzicka (78) reported that the frog's tongue, immersed in digestive juice, was no more rapidly digested when its blood supply was ligated than when it was left intact.

Working with dogs and rabbits, Sehrwald (79) tied off the stomach at both ends and filled it with a phosphoric acid solution; the changes in volume and acidity occurring after three hours were compared with those occurring in stomachs containing the same solution, but the blood vessels of which were perfused after death with soda solutions approximating the blood in reaction. He found that more neutralization took place in the dead stomach, and concluded that during life the neutralization of acid by the circulating blood does not follow the laws of simple diffusion. This made it necessary for him to accord recognition to the role played by the living cell in protecting the mucosa of the stomach from digestion by its juices, and he wisely suggested that autodigestion must be prevented in part by the alkalinity of the blood, in part by the activity of the living cell.

At this point we may mention, only for the sake of completeness, the contribution of Rassers (92); otherwise it should be ignored. He assumed, in order to establish a working hypothesis, that hydrochloric acid is produced by the reaction of sodium chloride with water: $NaCl + H_2O \rightarrow Na + OH + H + Cl$, and that HCl is excreted by the cell, leaving the NaOH in the cells to neutralize any HCl that might diffuse back, thus explaining why the stomach does not digest itself. (The same mechanism, Rassers asserted, would hold good for the alkaline secretions, where alkali would be absorbed and the acid left in the cells; this would refute the criticism repeatedly directed against the Virchow-Pavy theory—namely, that it did not account for the immunity of the intestine to the action of the pancreatic juice.) Rassers' evidence in support of his view was as follows: four dogs were fed a diet free of sodium chloride on the assumption that, in the presence of a chloride deficiency, the gastric glands could form little acid, hence a correspondingly small amount of sodium hydroxide would be present in the cells to protect the mucosa against the action of the exogenous acid-pepsin. When the blood chloride level began to fall, he fed the dogs 100 cc. of an acid-pepsin solution for three-day periods, omitting the feeding on one day between periods. When the dogs were sacrificed from the twelfth to the twenty-seventh day, the first two had hemorrhagic erosions of the stomach; the last two had small acute gastric

and duodenal ulcers. Controls consisted of two dogs on a salt-deficient diet; neither of these animals developed ulcer.

Theory of Protection by the Nutritive Function of the Blood

The Virchow-Pavy theory of the protective action of the buffering and neutralizing capacity of the blood should not be confused with the idea that the nutritive function of the blood, which maintains the life of the cells, is required to protect from autodigestion. All theories start with the observed fact that dead animal tissue is digested in time. All parenchymatous tissues after death undergo autolysis. Self-digestion of the stomach and intestine proceeds rapidly after death if gastric and pancreatic juice have been secreted prior to death, otherwise autolysis occurs.

The Localized Necrosis of Cells Results in the Formation of an Erosion or an Acute Ulcer. John Hunter, in 1772, recognized that the stomach may digest itself after death (1). Cruveilhier (80), who in 1821 first clearly described chronic gastric ulcer as a disease, recognized that in life a hemorrhage into the mucosa leading to localized necrosis of cells and loss of substance resulted in an erosion or an acute ulcer. With this idea in mind, Virchow (66) suggested that *aseptic vascular occlusion* of vessels in the mucosa or submucosa due to spasm, thrombosis, or embolism might be the cause of localized necrosis, which will be discussed in detail later.

There is no doubt, as will be shown later, that hemorrhages into the mucous membrane will cause erosions and acute ulcers. In such an instance, the cells are completely deprived of blood. However, the anastomosis of the blood vessels in the stomach is so rich that the stomach survives when all the vessels (arteries and veins) are tied along the greater curvature, and all or all but one along the lesser curvature; when the veins alone are obstructed, edema, erosions and acute ulcers occur which heal in a few days. However, these lesions could occur in the absence of acid-pepsin due to the sloughing of the necrotic tissue. When the arteries and veins to the stomach are tied as just indicated, the secretion of acid temporarily ceases. The resistance of such a stomach, deprived of most of its normal blood supply, to acid-pepsin has not been studied, so it cannot be stated at what level of diminution of the blood flow of the stomach the mucosa becomes less resistant to acid-pepsin.

Local Injury to Cells May Release Histamine Which May Cause Local Arteriolar Spasm and Decreased Resistance to Digestion. C. A. Dragstedt (81) has presented a novel idea to explain why living tissues may be digested by proteolytic enzymes, while isolated cells, such as yeast, are not. He points out that proteolytic enzymes release histamine

from cells, and that histamine is capable of producing angiotoxic phenomena, such as contraction of arterioles and increased permeability of capillaries, although histamine is not directly cytotoxic. He therefore postulates that the ability of proteolytic enzymes to digest organized living tissue may be dependent upon their ability to injure cells, which in turn releases histamine which impairs the blood flow locally and causes the cells to lose their relative resistance to digestion. If sufficient histamine is released locally in an area of the gastric and duodenal mucosa to cause arteriolar spasm, there is no reason to doubt that the improperly nourished cells would become susceptible to digestion.

Theory of the Resorption into the Blood of Digestive Ferments

As far back as 1884, Gaglio (82) complained that the physiologists were approaching the problem of autodigestion from a very restricted point of view; that is, their observations were limited to the stomach. He argued that since pancreatic juice is an equally active proteolytic substance which remains for some time in the intestine, investigators should give equal consideration to the question of why the intestine or pancreas do not digest themselves. From his experiments on the injection of gastric juice and pancreatic extract into the isolated urinary bladder of a rabbit, Gaglio concluded that the resistance to digestion is not a peculiar property of the stomach, but characterizes other living organs. After criticizing the existing theories, he offered the view that the digestive ferments, as they reach the cells, are absorbed into the blood stream and are thus prevented from destroying the tissues.

It was later shown by Langenskiold (30) that the mucosa of the urinary bladder *was* digested by either gastric or pancreatic juice; and the evidence already cited shows that enzymes probably are not absorbed from the lumen of the alimentary tract unless the cells are injured (p. 57).

It cannot be stated categorically that enzymes are not absorbed because of their protein nature and relatively large molecular size (83), since it is known that proteins may be absorbed from the intestine in quantities adequate to produce an allergic reaction (84). Nevertheless, there is no satisfactory evidence that any of the activated digestive enzymes are absorbed into the blood (85), though when the pancreatic duct is obstructed the pancreatic enzymes may be absorbed from the pancreas (85). If trypsin were absorbed in amounts adequate to overcome the antitryptic activity manifested by blood serum and organ extracts (86), it would probably cause necrosis, as indicated by the experiments of Northrop (14).

Theory of the "Biochemical Resistance" of the Living Cell

Before the turn of the century, the five then existing theories of the resistance of the stomach to autodigestion were sufficiently well crystallized to call forth a critical appraisal. This was supplied by Fermi (23, 87), who also presented a theory of his own. Fermi's objections to the current theories are outlined with our comments added in parentheses.

(1) Protection by the surface epithelium.
   (a) When the epithelium is lost, as in erosions or acute ulcers, there is no ensuing self-digestion. (Correct; if the epithelium were the crucial factor, then any breach in its continuity should inevitably lead to widespread destruction of underlying tissue.)
   (b) There is no reason why a thin layer of epithelium should be any more capable of withstanding gastric juice than large pieces of meat. (There are good reasons why living tissue should be more resistant to digestion than dead tissue.)
   (c) The healthy spleen is not digested when implanted into the stomach. (Not settled; see next chapter. But the epithelial surface of implanted intestine is not digested, whereas the serosal surface is.)

(2) The acid, immediately upon its formation in the cell, would be neutralized; hence none would be present in the gastric juice. (Not necessarily; the acid may be formed near the secretory surface [for rapid diffusion] or on the secretory surface of the cell. At any rate, there is a better objection; e.g., this theory does not explain the resistance of the intestinal mucosa to succus entericus and pancreatic juice.)

(3) Protection by mucus.
   (a) Mucus is present after death of the organ but does not prevent its postmortem digestion. (Mucus only retards digestion, and the digestion may start in the gland tubules where there is no mucus.)
   (b) During the digestive process, mucus is separated from various parts of the gastric surface as it envelopes the food, but the "bared" areas are not digested. (This is true, but mucus is continuously secreted and the mucous cells resist digestion more than muscle cells.)
   (c) When mucus is withdrawn artificially and gastric juice is poured into the stomach, there is no digestion. (When the

mucus is wiped off the pyloric mucosa, the mucosa is more sensitive to acid injury.)

(d) A piece of meat well covered with mucus is digested. (Digestion is definitely retarded if the meat is well covered with mucus.)

(e) Acid and pepsin are formed underneath, not upon, the layer of mucus. (Acid is, but it is not certain at what point pepsinogen is changed to pepsin.)

(f) The spleen is not digested when implanted into the stomach.

(4) Resorption of the ferments.

(a) If this theory is true pepsin would be absorbed into the blood as fast as it is produced; hence, none would be available for digestion.

(b) Enzymatic activity is too rapid, and the enzyme is too intimately attached to the substrate, to conceive of its being absorbed away. (This would apply until the substrate is digested unless the enzyme is also digested, which is true only to a slight extent for pepsin but to a greater extent for trypsin (88).)

Fermi rejected all the theories proposed and attributed the resistance of living cells to digestion to the peculiar configuration of the living protein molecule. Splendore (89) suggested that this characteristic consists of a sort of "negative chemotropism" which renders it impossible for the protoplasm to enter into chemical reaction with ferments. On purely theoretical grounds, Lumiere (90) similarly attributed the resistance of living cells to the chemical inertness of the colloids and micelloids of which they are composed.

Certain Organisms Live in the Digestive Juices

The sustaining point of Fermi's argument was the fact that many bacteria and parasites dwell and thrive in the gastrointestinal tract. Living Hyphomycetes and Blastomycetes are not destroyed by gastric juice, and Schizomycetes are not affected by trypsin (41). Living amebae are not digested by trypsin (14). Erythrocytes and spermatozoa are reported to be resistant to trypsin for several hours (93, 94). The earthworm, the larvae of flies, and intestinal worms are not affected by trypsin (41, 14). The earthworm, goldfish, and ascarid are attacked by neither trypsin nor pepsin (41, 14). Yet some bacteria and living animals are.

The cuticle of many animals is resistant to digestion because of their chemical composition. Fredericq (91) and Klug (41) found that the cuticle of Ascaris, even after boiling, resists digestion by trypsin and pepsin. This is also true of the egg membrane of some parasites (41) and of the

egg envelope of the hen, facts which are easily confirmed. These are instances, like the surface epithelium of the stomach, in which the chemical composition of the cell is such that it is not easily digested.

All Living Matter Shows Some Resistance to Digestion

It is now well known that all living matter shows some resistance to digestion. This is true not only of the membrane of cells but also of the protoplasm; for example, it is well known that raw egg white is difficult to digest.

Autolysis due to the action of enzymes within the cell occurs after the death of the cell. The chief difference between autolysis of a cell after death and the digestion of a killed cell by pepsin and trypsin is the rapidity with which the latter occurs. It is also well known that the selective permeability of the cell is one of the remarkable attributes of the living cell, and that this attribute disappears with death or injury (95). Why, in the case of those cells which are known to resist tryptic and peptic digestion and are not chitinous, the enzyme does not act on the surface membrane is conjectural. The evidence available indicates that the surface membrane of animal cells is not protein in nature, though it may contain some protein; it reacts as though it is rich in lipoids, because fat solvents pass through so readily. The tiny lipid particles, or chylomicrons, in blood are believed to be stabilized by a protein film because the first zone of aggregation of the particles occurs at approximately the isoelectric point of the blood proteins (about pH 5.0) (96). Inasmuch as this is also the critical pH level for many types of cells, it may be that a similar protein-lipid system exists in the cell membrane.

Each type of cell manifests its own permeability characteristics which vary during life and with rest and activity of the cell. While proteins and substances of large molecular size do not readily penetrate most cell membranes (the alimentary proteolytic enzymes are proteins), an increased permeability might permit such proteins to penetrate the membrane; thus the observations of Driver and his associates (97) indicate that substances which increase the permeability of cells render the intestinal mucosa more susceptible to digestion. One would think that the bile salts, which are surface active substances, would predispose to autodigestion; yet bile salts are claimed to inhibit pepsin.

Sensitivity of Cells to Acids and Alkalies

It is appropriate to inquire regarding the effect of hydrogen and hydroxyl ions on the permeability of cells and the protoplasm of cells. Such information applies not only to the surface epithelium but also to the underlying muscle and connective tissue cells which are exposed when

an acute ulcer is produced. It applies to the fibroblasts which proliferate and form granulation tissue over which the epithelial cells grow to cover the defect.

In general, living cells are not exquisitely sensitive to changes in hydrogen ion concentration of their milieu because H^+ and OH^- ions penetrate slowly. When they do penetrate, they meet with the buffer systems (buffer salts and protein) in the cell and are neutralized, especially in the presence of a good blood supply. It is generally true that weak acids and bases (amino acids, fatty acids, carbonates and bicarbonates) penetrate cells more readily than strong acids and bases (HCl and NaOH) unless toxic concentrations of the latter are approached; the amino acids, and fatty acids as soaps, penetrate cells quite rapidly. Relatively wide ranges of carbonate and bicarbonate are tolerated in body fluids. However, some cells are quite sensitive to changes in pH; the blood vessels react to a change of from 0.05 to 0.2 pH unit. The cells of the carotid sinus, respiratory, and vasomotor center are sensitive to small changes in pH and the H_2CO_3 concentration of the blood. Other cells such as connective tissue cells are quite insensitive (95).

Limits of Tolerance of Cells to Acidity and Alkalinity

Gastric juice contains HCl, a strong acid, which penetrates cells slowly. Pancreatic juice contains $NaHCO_3$, a weak base, which penetrates cells relatively rapidly but is more readily buffered. There is, however, a limit to the tolerance of cells to acids and alkalies and some information is available on this point which bears on the ulcer problem.

According to Fischer (99) and Lewis and Felton (98), fibroblasts from embryonic chicks grow between pH 5.5 and 8.5 in a tissue culture, the optimum pH being 6.8 to 7.8. The younger the embryonic tissue the better the growth in more acid media, but growth does not occur below pH 5.0. According to Barta (100), mammalian fibroblasts grow between pH 7.2 and 9.5, but he did not go below 7.2. Phagocytosis by leukocytes is decreased beyond the range of pH 6.3 to 7.6. The reaction of healthy granulation tissue under scabs, which prevents alkalinity due to loss of CO_2, ranges from pH 5.8 to 7.05, and a slight acid reaction favors growth or healing (101). Strong acids (HCl) injure and penetrate the membrane of a muscle fiber when the pH is 5.7 (101) and irreversible coagulation and death (acid contracture) occur when the pH of the solution (HCl) is 4.0 (102). With strong alkalies (NaOH) irreversible coagulation and death of muscle occurs at a pH of from 11 to 12 (103). In studying the effect of drugs on intestinal muscle strips, saline solutions having a pH of 8.0 are frequently employed. It is of interest that the isoelectric point (i.e., the pH at which proteins become least soluble) of cellular proteins, such as glob-

ulin (pH 5.4–5.5), albumin (pH 4.8), myogen (pH 6.2–6.4), and myosin (pH 6.2–6.6), approximates the pH at which strong acid produces death of muscle cells and fibroblasts. Bradley (104) points out that the critical point at which autolysis or digestion of a protein starts is just above the isoelectric point. For example, the isoelectric point of serum albumin is pH 4.7 and the critical point at which it becomes digestible is pH 5.0. The phagocytosis by leukocytes is decreased by any marked departure from neutrality (range pH 6.2–7.6) (105).

The pH of 0.1N HCl, or of strongly acid gastric juice is 1; of 0.05N HCl, 1.32. In titrating gastric juice, it is customary to state that free acid is present when the pH is below 4.0, or Topfer's reagent is pink. The pH of pancreatic juice ranges from 8.0 to 8.6, and rarely reaches 9.0. With these facts in mind and the foregoing data on the pH at which acids and alkalies injure cells, there is little wonder that, in the case of the gastrointestinal tract, "peptic" rather than "tryptic" ulcers occur. It also is evident that when free acid (pH lower than 4.0) is present in the gastric contents the muscle cells and fibroblasts exposed by acute ulceration could be destroyed unless protected by a transudate from the blood (fibrin, albumin, globulin, and buffer salts) and a supply of nourishment.

Only a Small Portion of the Cell Is Exposed to the Digestive Juices

It should be pointed out that only a part of the surface of a cell in the mucosa is exposed to the digestive juice and that the opposite surface is exposed to the tissue fluids which nourish it. For example, Northrop (14) has made the following calculation: Given a cell equivalent to a 1,000μ cube containing protein molecules each equivalent to a 10μ cube, one surface layer of the cell will contain 10,000 molecules of protein whereas the entire cell contains 1,000,000 molecules of protein. Thus, the digestion of the block from the surface will be only one one-hundredth of the whole cell. Hence, sublethal injury of the surface could occur provided the cell could repair its surface as rapidly as injured or digested.

It is well known that living, well-nourished cells can repair a sublethal injury of its membrane and that sublethal injury may be a stimulus to the secretion of protective fluid derived from the blood, to mitosis of the cell, or to mitosis of surrounding cells (95).

Theory of Protection by Antiferments

In 1901, Danilevski (106) found that if minced organs, especially gastric mucosa, were digested with 0.3 per cent acetic acid, the filtrate would inhibit peptic digestion. He proposed that the active ingredient opposed autodigestion. In 1903, his student Hensel (107) found that an extract of

the gastric mucosa of pigs strongly inhibited peptic digestion and called the active principle "antipepsin" but said it was not an "antiferment" because it resisted boiling and was not precipitated by lead acetate and 6 volumes of alcohol.

In 1902, Weinland (108) extracted the tissue juice of *Ascaris*, and found that it possessed antipeptic and antitryptic activity. He concluded that the antiferments rendered it possible for the parasites to resist peptic and tryptic digestion. His active principle was destroyed by heating at 95° C. for 10 minutes. He reported that the antiferment did not destroy the enzyme but prevented its action. He (108) also found antipeptic activity in extracts of the gastric mucosa and antitryptic activity in extracts of the intestinal mucosa of the pig.

The reports of Weinland (108, 109) stimulated considerable investigation on the presence of "antipepsin" and "antitrypsin" in gastric and intestinal mucosa. Extracts or preparations were made by a number of authors, who attached more or less specificity to the phenomenon (110–112, 32). Klug (41) ascribed the antipeptic and antitryptic activity to mucus. Bayliss (113) and Hamill (114) could not confirm the existence of antitryptic activity in intestinal mucosa, but Hamill observed antipeptic activity in gastric mucosa. Langenskiold (30) observed the antipeptic activity of various tissue extracts and concluded that the evidence did not demonstrate the existence of a specific antipepsin and that the inhibitory effects of the extracts can be explained in all experiments as due to the presence of albumoses, peptones, and in some cases to inorganic salts and changes in reaction of the digest. Katzenstein (31, 115) considered "antipepsin" to be active only in an alkaline medium, a rather ridiculous assumption since pepsin has only the slightest activity at a pH of 4.0, the pH for optimum activity being 1 to 2.2.

Several papers appeared purporting to show that peptic ulcer was due to an imbalance between pepsin and "antipepsin" (114–116). Antipepsin has been reported to be absent from the blood serum of ulcer patients and to be present in normal subjects (117). This latter report was not confirmed by Orator who examined the blood of 50 patients operated upon for peptic ulcer (118). Wolff (119) found no difference in antipeptic activity of the gastric mucosa of patients with and without gastric ulcer.

The Antipeptic Activity of Plasma and Tissues Is Not Due to a Specific Antipepsin in the Immunologic Sense

Since pepsin is denatured at the alkaline reaction of blood, one should not expect to obtain an antipepsin in the sense of a specific antibody. After the injection of Northrop's crystalline pepsin, precipitins are obtained

only for the denatured pepsin (120). The crystalline trypsin of Northrop which is not denatured by the alkalinity of the blood forms precipitins, and anaphylactic reactions can be produced with trypsin and chymotrypsin (121). Thus, trypsin can form an antitrypsin in the immunologic sense but pepsin cannot. However, an antipepsinogen can be produced. It has not been shown that the antipeptic or antitryptic activity of the blood serum or tissue fluids is an antibody in the immunologic sense (122, 123).

Nonspecific Inhibitors of Peptic and Tryptic Activity

Nonspecific inhibitors of peptic and tryptic digestion and other enzymes are known to exist (122, 124). Peptones (124), mucins (48), chondroitin and mucoitin sulfuric acid (125), blood serum, edema fluids, and extracts of bacteria (86) inhibit peptic activity, probably by adsorption of or a loose combination with the pepsin. The inhibition of autolysis by serum proteins occurs when whole serum is used or when repeatedly crystallized serum globulin or albumin is used. This type of inhibition is therefore due to the protein itself and not to some other substance (104). Northrop and his colleagues (88) have carefully studied an inhibitor of pepsin, which is produced during the autocatalytic conversion of pepsinogen to pepsin; and an inhibitor of trypsin, found in pancreatic tissue, has been crystallized. The inhibitors studied by these investigators have the properties of a polypeptide, and form dissociable compounds with the respective enzymes. The pepsin inhibitor dissociates from the pepsin at a pH of less than 5.4, so that its action can be demonstrated only by the inhibition of the milk clotting action of pepsin. Furthermore, this pepsin inhibitor is rapidly digested by pepsin in an acid medium below pH 4. Therefore it is unlikely that this particular pepsin inhibitor is of any importance in protecting the stomach from self-digestion, however it is probable that as yet unidentified pepsin inhibitors exist.

Thus, there are a number of substances which inhibit the action of pepsin and trypsin. Yet it cannot be concluded on the basis of the evidence available that any of these substances are specific, with the exception of Northrop's pepsin and trypsin inhibitor (88). The inhibitory action of mucous and mucoid secretions can be considered specific in an adaptive sense, and this merits emphasis. The kinetics of this reaction deserve study. Gastric juice contains a potent pepsin inhibitor which forms a pepsin inhibitor complex that dissociates upon dilution (141). The nature of this pepsin inhibitor is unknown; it is probably not mucus because the inhibitory action of mucus is not great enough to account for the inhibition of pepsin observed in gastric juice. The secretion of Brunner's glands inhibits peptic activity in a degree comparable to pyloric gland secretions.

A Consideration of the Resistance of Tissues to Pancreatic Juice and Its Enzymes

In the foregoing discussion consideration has been given to the proteolytic enzymes with particular emphasis on pepsin and hydrochloric acid. From the viewpoint of chronic peptic ulcer the emphasis is properly placed because there is no evidence indicating that pancreatic juice is concerned. However, to complete the analysis the pancreatic juice could be considered.

The Pancreas Digests Itself Under Certain Conditions

When the pancreatic ducts are mechanically obstructed in the absence of infection, the exocrine cells of the pancreas atrophy and many entirely disappear. This is said to be due to a pressure atrophy and necrosis. During the process, pancreatic lipase (olive oil splitting) and amylase are found in the blood and apparently cause no marked injury. The presence of pancreatic trypsin in the blood has not been satisfactorily demonstrated (85). Here is an instance of self-digestion or autolysis which causes no injury, except that resulting from the loss of the digestic function of pancreatic juice, since the fatty liver that results can be prevented by feeding raw pancreas, pancreatic juice, choline, or lipocaic (126, 127). It is not known whether the disappearance of the cells is due to autolysis by the enzymes found in pancreatic juice or by other intracellular enzymes, as occurs in the liver, salivary glands, and kidney when the ducts of these organs are obstructed.

Acute pancreatic necrosis or acute hemorrhagic pancreatitis represents a fulminating autodigestion of the organ by its own secretions (128–132). The pancreas undergoes a rapid autolysis with hemorrhage, apparently due to digestion and rupture of the wall of small blood vessels. To what extent the hemorrhage is due to the actual digestion of the wall of the blood vessels or to an obstruction of the venous return due to acute inflammatory swelling of the gland is uncertain. Whether the hemorrhage is primary or secondary in the course of the disease is also uncertain. Experimental infarction causes only a localized necrosis. A popular theory maintains that the regurgitation of bile from the common bile duct into the pancreatic duct, with some factor which ruptures the ducts and permits entrance of pancreatic juice to the interstitial tissues, is the cause (133–134). The relation of hemorrhage to the fulminating necrosis is of interest because in the slow atrophy and autolysis due to obstruction of the duct, which is not serious, the circulation is intact. In acute interstitial pancreatitis there is no hemorrhage and the necrosis is slight, though fat necrosis confined to the pancreas may be present; the circulation in this

instance is not markedly impaired and the condition is not serious. This is of interest in relation to peptic ulcer because erosions and acute ulcers are so frequently due to hemorrhage into the mucosa.

Autodigestion of the pancreas occurs soon after death (135). In our experience postmortem digestion of the pancreas does not occur as rapidly as postmortem digestion of the gastric and intestinal mucosa, unless antemortem hemorrhages have occurred into the organ.

The Intestine Will Digest Itself Postmortem and When Injured

The intestines are known to be digested quickly after death. In fasting, the tips of the villi are digested in the mouse (136) and rat, but no striking changes occur in the dog (137, 138). In the mouse the tips of the villi regenerate in 10 to 12 hours after realimentation (136). When the villi are injured, they are rapidly digested and regenerated, according to our observations, like the cells of the superficial epithelium of the stomach. Closed loops of the intestine, in the absence of pancreatic juice, ulcerate and perforate when the pressure in the lumen rises sufficiently to interfere with venous outflow (139). The rate at which the superficial cells of the villi are replaced under normal conditions of digestion is unknown.

The Drainage of Pancreatic Juice into the Stomach and Colon Does Not Cause Digestion of the Mucosa, Whereas Its Presence in the Gallbladder Does

It is not surprising that the drainage or regurgitation of pancreatic juice into the stomach does not cause digestion of the mucosa, because the acidity of the gastric juice quickly neutralizes the alkali and inactivates the enzymes. Even in the upper duodenum, the pH of the contents is less than 6.0 in most instances, and it is rare to find a pH of 7.0 or a neutral or alkaline reaction (142, 143). Trypsin manifests little or no proteolytic action at or below a pH of 6.0, except in the case of gelatin (88).

Also, the acidity of gastric juice is relatively greater than the alkalinity of pancreatic juice. It is very rare for the pancreatic juice to be more alkaline than pH 9.0. This pH is equivalent to 0.00001N solution of NaOH, whereas gastric juice has an acidity of 0.1N or 0.05N. On the basis of the relative acidity of gastric juice and the alkalinity of pancreatic juice, the latter should be expected to be less injurious to cells.

When pancreatic juice directly enters the colon from the duodenum in the course of otherwise normal digestion, the mucosa of the colon is not damaged (144). However, when the colon, devoid of contents, is perfused with pancreatic juice, erosions occur (145).

The gallbladder is claimed to be particularly sensitive to injury by pancreatic juice (146, 147). More recent experiments have not confirmed this. However, according to our experience, the gallbladder mucosa is sensitive to injury by solutions innocuous for other mucous membranes. It is injured by perfusion with 0.85 per cent NaCl solution. It has apparently been isolated so long in the evolutionary process from contact with any fluid other than bile that it is readily injured by foreign fluids.

There Is No Evidence Showing That the Pancreatic Enzymes Are Absorbed from the Lumen of the Bowel

As indicated above, the observations of Northrop (14) indicate that trypsin is not absorbed by living cells. There is no direct evidence showing that trypsin is absorbed from the lumen of the intestine. Crandall (85) found no evidence indicating that lipase and amylopsin are absorbed from the intestines. These observations, together with the fact that the alkali in pancreatic juice is a weak one, help to explain why the intestinal mucosa is not digested by pancreatic juice.

Also, as indicated above, the "antitryptic" power of serum and tissues does not appear to be due to a specific antitrypsin. Necheles, Ling and Fernando (151), who reviewed the literature, observed no increase in the antitryptic power after the parenteral administration of pancreatic juice or tissue. This indicates that trypsin is not absorbed, since if it were specific antitrypsin should be produced and increase the "antitryptic" action of the blood. However, it is claimed that the "antitryptic" power of dog's serum decreases steadily after pancreatectomy (148, 149), though it never completely disappears. The blood protein level was not followed.

We are not familiar with any work that has been done on the concentration of alkali required to injure the intestinal mucosa.

Other Enzymes

There is no evidence that the amylopsin in pancreatic juice is corrosive to tissues.

If steapsin, or the pancreatic lipase, escapes into the pancreatic or omental tissue, fat necrosis occurs. The cause of fat necrosis has been studied extensively. The results show that pancreatic lipase, free of trypsin, can cause fat necrosis (135, 150). Since pancreatic tissue and leukocytes contain a kinase similar to enterokinase, trypsinogen when it enters tissue may be changed to trypsin and facilitate the digestion of fatty tissue by pancreatic lipase (135).

Adaptation of the Surface Epithelium and the Gland Tubules to the Secretions and Secretory Mechanisms in Relation to the Nature of the Resistance of the Mucosa to Autodigestion

It is reasonable to assume that in the process of natural selection the epitheliums exposed to the digestive juices have become especially adapted to the digestive fluids which bathe them.

Stomach

The results of Bernard's experiment on the frog and clinical observation demonstrate that the skin is much more susceptible to the digestive action of the gastric juice than the epithelium of the stomach and intestine. Similarly, the skin is more susceptible to pancreatic juice than the intestinal mucosa. The gradient of susceptibility to acid-pepsin in the gastrointestinal tract and the marked susceptibility of the mucosa of the gallbladder to pancreatic juice serve to emphasize the point. The mucus-secreting epithelium provides a special protection against mechanical and chemical irritants and acid-pepsin.

Intestine

The intestine, however, is devoid of a continuous layer of mucus-secreting epithelium, very probably because such an epithelium would seriously hamper absorption. Yet, the intestine is adapted to dilute, neutralize, and buffer acid fluid entering it from the stomach. An alkaline mucoid fluid is secreted rather copiously by the glands of Brunner. When acidified it inhibits peptic activity to the same extent as the mucus secreted by the pyloric mucosa (140). A slightly alkaline fluid with buffers for acid is secreted by the intestinal cells in the crypts of Lieberkühn. Both bile and especially pancreatic juice are alkaline, and both contain buffers for acid.

The glands of Brunner appear to play a crucial role in the determination of the gradient of susceptibility from the duodenum to the ileum and in protecting the mucosa of the duodenal antrum or bulb. This mucosa, unlike the stomach, is not covered with a continuous layer of mucus-secreting epithelium; it nevertheless receives the brunt of the acid-pepsin insult and the mechanical force of the ejected chyme. The pancreatic juice and bile, entering lower, probably provide greater protection for the mucosa of the more distal portions of the duodenum than for the duodenal antrum. That pancreatic juice does regurgitate to the duodenal antrum and play a role in neutralization and dilution is indicated by the fact that the exclusion of pancreatic juice from the intestine predisposes to

the formation of duodenal ulcer. From this analysis it appears that the mucosa of the duodenal antrum is the place most likely to be injured if the glands of Brunner and pancreas secrete inadequately.

There apparently is no known secretory mechanism or fluid to protect the intestinal mucosa from the digestive action of pancreatic juice. The mucus secreted by the goblet cells may serve to some extent. However, the alkalinity of pancreatic juice never becomes adequate to injure the intestinal cells and permit digestion in the presence of an adequate blood flow. The pH of the intestinal contents is rarely greater than 7.5. The weak alkali in pancreatic juice is adapted to a mucosa which has no special protective layer of epithelium and which secretes a fluid that protects only by diluting and buffering.

Adaptations of the Gastric Gland to HCl-Pepsin

Bernard believed that the HCl was secreted by the gastric glands in a combined form and was released as free acid only in the lumen of the stomach. If this were the case, then the cells lining the gastric tubule would not be subject to contact with a digestive fluid. However, the evidence indicates that this is not true.

Bocci (77), in 1880, made the following suggestion when he observed that the injection of gastric juice beneath the mucosa of the stomach would cause localized digestion of the tissue. He proposed that the immunity of the cells of the gastric tubule to autodigestion is due to the "admirable hydraulic succession" of secretory events, that the pepsinogen and HCl, neither active alone, are secreted alternately by the gland and are activated only after reaching the surface of the lumen of the stomach where mucus acts as a protective barrier. There is no evidence in support of Bocci's proposal (69, 70).

Acid and pepsinogen are secreted simultaneously, the acid by the parietal cell and the pepsinogen, the precursor of pepsin, by the chief cells. The chief cells are especially concentrated about the base of the gland tubule, the parietal cells near the apex or neck of the tubule (Figs. 11 and 12). The parietal cell has an extensive intracellular canalicular apparatus which, apparently by increasing the surface of the cell, facilitates the elimination or formation of the acid (Fig. 18).

Michaelis (83), in 1926, advanced the following explanation: "Why does not the acid pepsin-containing gastric juice digest the wall of the living stomach itself? It seems to me that this problem no longer involves any difficulties. It is virtually certain, from a histological aspect, that the acid and the pepsin, though produced in the same glands, are not produced in the same cells. Some cells may secrete acid, others pepsin. The mixing takes place only in the cavity of the stomach. Now the superficial cell

membranes, which regulate the permeability of any cell, seem to consist of some lipoid substance. Obscure and equivocal though this term may be, at least it is not a protein which may be subject to the action of pepsin. So, the membranes of the mucosa being indigestible, and certainly also impermeable for a molecule of such a large size as that of pepsin, will pre-

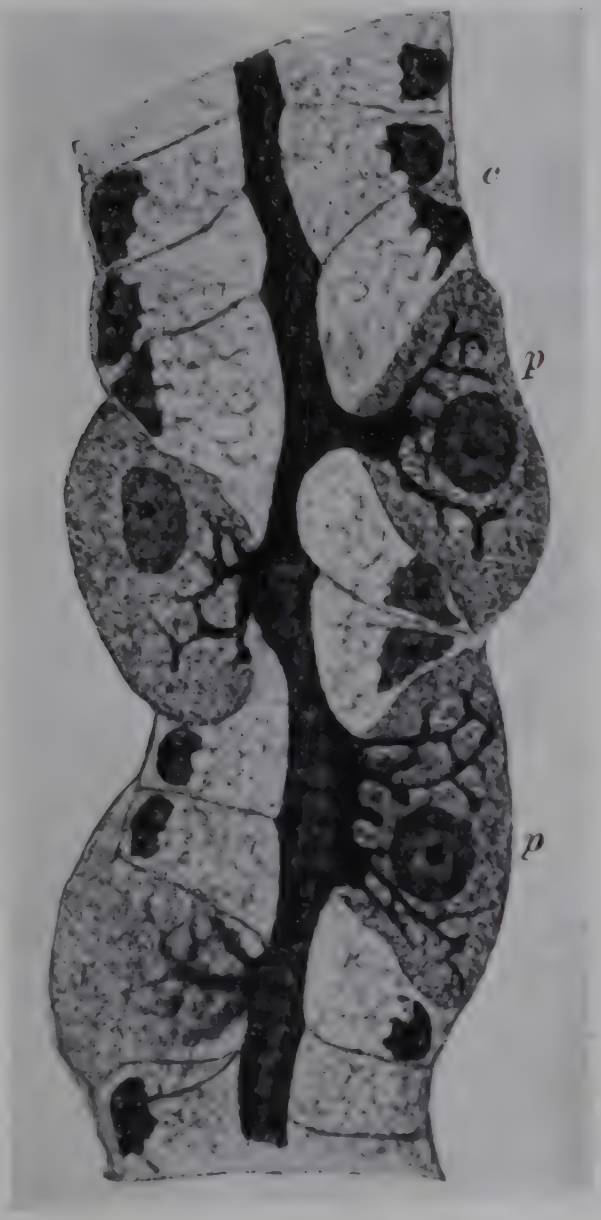


FIG. 18. A section of a portion of a fundic gland tubule showing the intracellular canalicular apparatus of the parietal cell (*p*) connecting with the gland tubule. The cells adjacent are body chief cells (*c*) which form and secrete pepsinogen. (Courtesy, Zimmerman: *Arch. f. mikr. Anat.*, **52:** 552.)

vent the interior of the cells from being digested as long as the membrane is intact." The explanation of Michaelis is incomplete on two counts. *First*, the pepsinogen is mixed with acid in the gland tubule. Whether the pepsinogen is changed to pepsin in the tubule or only in the lumen of the stomach is uncertain. At 0° C. acid slowly activates pepsinogen; at room temperature (about 20° C.) the activation is so rapid that its isoelectric point cannot be determined. So this suggests that at body temperature an appreciable portion of pepsinogen is changed to pepsin in the gland

tubule. *Second*, he failed to consider the repeatedly confirmed experiment of Pavy in which it was shown that when a patch of the mucosa is removed healing occurs rather rapidly.

As indicated previously, the integrity of the cell membrane regardless of the source of the cell is important. Pepsin, according to the evidence, cannot enter the cells lining the gastric tubule unless their membranes are injured. The remarkable fact, however, is that the cells lining the gastric tubule are so very impermeable and resistant to HCl. All recent evidence (69, 70) indicates that the parietal cell forms a 0.58 per cent HCl solution (pH 0.83). If the juice were secreted and then quickly squeezed out, such a mechanism might protect the cells lining the tubules; this, however, is very unlikely. In excised specimens acid diffuses more rapidly from the parietal cell than from the lumen of the tubule (9). Even if the juice is discharged from the tubule before sufficient time has elapsed to activate pepsinogen, we still must explain why the cells lining the tubule are apparently so resistant to acid.

Michaelis (83) points out a very important adaptation regarding the nature of the secretory processes involved in the secretion of gastric juice. It is basic to the reason why the cells in secreting gastric juice are not digested; namely, the HCl and pepsinogen are secreted by different cells. If they were not, the pepsinogen would be activated in the presence of HCl, and digestion presumably would occur. Nevertheless, some lower forms are said *not* to possess distinctly identifiable acid and pepsinogen-secreting cells. It has been presumed that a single cell secretes both acid and pepsinogen (61). Either the histologic technique is inadequate to reveal a cell which secretes acid and another which secretes pepsin, or these forms possess a very remarkable cell, a cell which secretes free acid in a combined form, or a pepsinogen that is slowly activated at the normal body temperature of the animal.

The limited extent of tolerance of surface epithelium of the stomach to acid-pepsin, indicated above, emphasizes the possible deleterious effect of a hypercontinuous secretion or an abnormally prolonged gastric secretory response to a meal or a stimulus. In this relation the relative amount of secretion of diluting fluid by the gastric mucosa and the extent of entero-gastric regurgitation of the alkaline duodenal fluids is significant.

Adaptations of the Pancreatic Cell and Tubular Epithelium to Its Secretion

In the case of the pancreas, the bicarbonate solution and enzymes are secreted by the same cells according to current theory (Fig. 19). The trypsinogen, however, is not activated normally until it reaches the lumen of the intestine where it is activated by the enterokinase in the intestinal

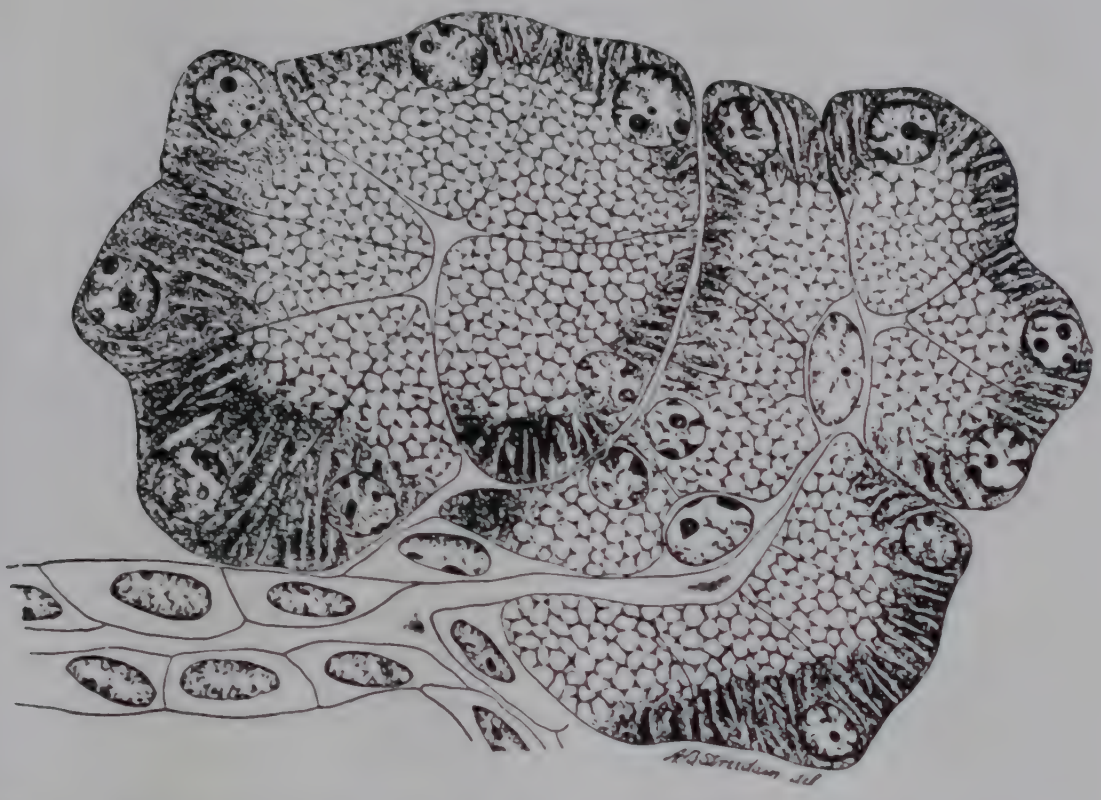


FIG. 19. Two pancreatic acini, in one of which the tubule draining the acinus is shown. The oval, clear spaces of the central half of the cell are zymogen-containing spaces. Sometimes the tubule invaginates into the cell, giving the appearance of an intracanalicular apparatus. Farther down the tubule, goblet cells are found. 1555X. After Bensley. (Courtesy, Maximow and Bloom: "Textbook of Histology," W. B. Saunders Co.)

juice. This is a beautiful example of adaptation. The cells which form the secretion and the epithelium lining the pancreatic tubules and ducts are not exposed to an active proteolytic enzyme. However, the lipase is active in the bicarbonate solution secreted by the pancreatic acinar cell and there is fat in the protoplasm of the acinar cell. Why is it not digested? If the bicarbonate is formed at the surface of the cell membrane, or by cells other than those which secrete the enzymes, then our question would be adequately answered. If this is not true, then, as in the case of the cell in lower forms which is supposed to secrete acid and pepsin, we are confronted with explaining how a cell can form a digestive fluid without digesting its protoplasm. This immediately brings to mind the digestive vacuole in the *Ameba*.

After the pancreatic juice is in the tubules, the epithelium of the tubule is not injured by the weak alkali of the juice and the cells, unless injured, do not absorb the enzymes. Goblet cells, which secrete mucus, are found interspersed among the cells lining the ducts and larger tubules.

Summary

Stomach

It is impossible during life for pepsin to be absorbed due to the properties of the cell membrane. The cell membrane must be injured before acid and pepsin can enter.

Acid and pepsinogen are secreted by different cells lining the tubule of the gastric gland. The pepsinogen is quite rapidly changed to pepsin by acid; whether it is completely converted to pepsin before it enters the lumen of the stomach is uncertain. The acidity of the fluid in the gastric tubule may be as great as 0.58 per cent (pH 0.83), an acidity which if present for 6 or 12 hours is reported to injure even the mucus-secreting surface epithelium of the stomach. Even if pepsinogen is not activated in the tubule the cells lining the tubule appear to possess a remarkable resistance to acid injury. When the acid-pepsin is in the lumen of the stomach, it is in contact with mucus and a continuous layer of mucus-secreting epithelium, both of which are resistant to digestion. The limit of resistance of the surface epithelium to acid will be dealt with in Chapter 10 where it will be pointed out that the strength of the acid and the duration of its action influence the results. An acidity of 0.00036 per cent (pH 4.0; 0.1 clinical units 0.0001N) coagulates muscle cells and stops the growth of fibroblasts.

An active circulation through the mucosa is requisite for resistance to digestion. If a hemorrhage occurs into the mucosa, the area sloughs or is digested. If an arterial spasm occurs or if there is venous stasis, digestion could result. An active circulation not only maintains the nutrition of the cell but permits renewal of the cell substance, its secretion and proliferation. It undoubtedly supplies base for maintaining the reaction of the cell. In addition to this, when tissues beneath the surface epithelium are exposed, inflammation occurs, plasma exudes providing a protective coat of fibrin, bases for neutralization, and protein buffers for acid or alkali. A good nutritive condition is required for the regeneration and proliferation of cells and mucous secretion. In contrast to the skin, the mucosal cells of the stomach are adapted to gastric juice, an adaptation which is probably dependent on a difference in the structure and composition of the cell membranes.

Intestine

The duodenal mucosa is protected from injury by acid-pepsin and from autodigestion by the secretion of the glands of Brunner, the intestinal juice, pancreatic juice, and bile. These secretions are alkaline and serve to neutralize, buffer, and dilute the acid which inactivates or inhibits

peptic digestion. In the absence of injury, the cells do not absorb pepsin and acid and are not digested. The alkali in the juices is chiefly $NaHCO_3$ which is a weak alkali in contrast to HCl which is a strong acid. For these reasons the alkali of the pancreatic juice is unlikely to injure the cells and cause digestion of the intestinal mucosa. In contrast to the skin, the cells of the intestinal mucosa are adapted to the pancreatic juice, an adaptation which probably is dependent on a difference in the structure and chemical composition of the membrane of the cells. In addition, the alkalinity of the pancreatic juice is rapidly reduced by neutralization and dilution by the gastric juice and dilution by the intestinal juice. An active circulation through the mucosa is essential for the maintenance of the resistance of the intestinal cell to autodigestion. A good nutritional condition is requisite for the regeneration and proliferation of the cells of the intestine.

Pancreas

The pancreatic juice is a weak alkaline solution which in itself is not particularly injurious to cells. The trypsin is secreted in an inactive form, trypsinogen, which normally is not activated until it reaches the lumen of the intestine. The lipase which is secreted in an active form is not absorbed by the uninjured cells of the tubules and ducts, which also applies to amylopsin and trypsinogen. An active circulation is requisite for the prevention of a fulminating autodigestion of the pancreas when the ducts are obstructed or injured so as to allow the passage of activated enzymes into the interstitial tissues.

Conclusions

The stomach does not digest itself when its circulation is adequate, when the tolerance of the cells to acid-pepsin is not exceeded, and when the nutritional condition of the subject is adequate for the regeneration and proliferation of cells of the gastric mucosa and for mucous secretion.

The intestine does not digest itself when its circulation is adequate, or when the diluting, neutralizing, and buffering reactions between the gastric juice, Brunner's secretion, intestinal juice, bile, and pancreatic juice are normally maintained within the limits of tolerance of the mucosa to acid-pepsin and active pancreatic juice. The general nutritional condition must be adequate for the regeneration and proliferation of the cells of the intestinal mucosa.

The pancreas does not digest itself when its circulation is adequate, when the trypsinogen in the organ is not activated, and when lipase does not escape from the cells or ducts into the interstitial tissues. When the ducts are obstructed, a slow atrophy and autolysis of the pancreatic acinar cells occurs which is not injurious because of an active circulation.

The gastrointestinal mucosa displays a gradient in its susceptibility to injury by acid-pepsin. Those portions of the tract which normally are most exposed to acid-pepsin show the greatest resistance; the farther the mucosa is removed from the site of formation of acid-pepsin the greater is its susceptibility to damage. In the upper gastrointestinal tract special mechanisms help to account for the gradient of susceptibility (mucus secretion, Brunner's glands, pancreatic juice, and bile). In the lower intestine the increasing susceptibility of successively lower segments must be attributed to lack of adaptation of the lining cells to acid-pepsin. The nature of this adaptation appears to depend on the cell membrane and the extent of its resistance to injury by acids and alkalies.

The resistance of the cells to digestion may be reduced by a sublethal injury or an injury which does not cause death of the cell.

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OUTLINE OF CHAPTER 5

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III. Intestine

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B. intestinal mucosa

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CHAPTER 5

Implantation of Organs into the Stomach

Introduction

It was pointed out in the previous chapter that one approach to the basic problem of the resistance of the stomach to autodigestion is to determine whether this resistance is a specific biologic characteristic not shared by other living organs of the body. There has been enough investigation of this question, and its bearing on the etiology of peptic ulcer is of sufficient importance to require separate consideration.

Spleen

Apparently the first investigator to implant living tissue into the stomach was Bocci (8), who sutured the omentum into the stomach of a rabbit. After several days, during which the rabbit appeared normal, the animal was opened and the omentum found mostly necrotic. Bocci could not decide how much of this was due to the fact that the organ had wound up and contracted upon itself, and how much was due to the action of the gastric juice. Therefore, he turned to an organ which could not wind upon itself; namely, the spleen. This was exposed to the action of the gastric juice by placing part of it inside the stomach; the rabbit resumed eating within a few hours after the operation, and was killed on the third day. The spleen was found mostly digested. This experiment was repeated in dogs and cats by Viola and Gaspardi (43); in observations on 18 animals surviving from 12 to 64 hours, they found that the spleen was not digested. Assuming that the blood supply to the spleen was not impaired in Bocci's experiment, it would seem that the disagreement could be attributed to the difference in the length of the observation period, but later reports make it apparent that the explanation is not so simple.

Kathe (21) implanted the end of the spleen into the stomach in three dogs. In the first dog, killed 33 hours after operation, the surface of the splenic capsule was digested; after seven days, there was beginning growth of gastric epithelium over the edges of the spleen; in the dog sacrificed on the twenty-first day, there was considerable digestion of the spleen with hemorrhage. These results were confirmed by Katzenstein (22) in two dogs examined at the end of 12 days and three months, respectively.

On the other hand, Licini (26) reported no digestion of the spleen in two dogs after 10 and 30 days when the organ was exposed to the gastric juice by attaching it to a window in the stomach; this was confirmed by Kawamura (24). Dragstedt and Vaughn (14), using the same principle, showed that there was no digestion of the spleen up to three months, even when the capsule was removed and the pulp exposed. But when implanted into a window of an isolated stomach pouch from which the secretions were prevented from draining by plugging the opening, the spleen was promptly digested (13). These experiments indicate that (a) the acidity of the gastric contents and (b) their prolonged action are important factors. A more decisive factor was identified by the investigations reported by Price and Lee (37). They demonstrated that when an organ is implanted tangentially into the stomach wall, little or no digestion takes place. But in three dogs in which 4 cm. of the inferior pole of the spleen was implanted so as to project into the lumen of the stomach, digestion of the implanted portion was complete when the animals were sacrificed on the nineteenth, twenty-eighth, and thirty-second days (Fig. 20). Obviously projection of the organ into the lumen favors digestion.

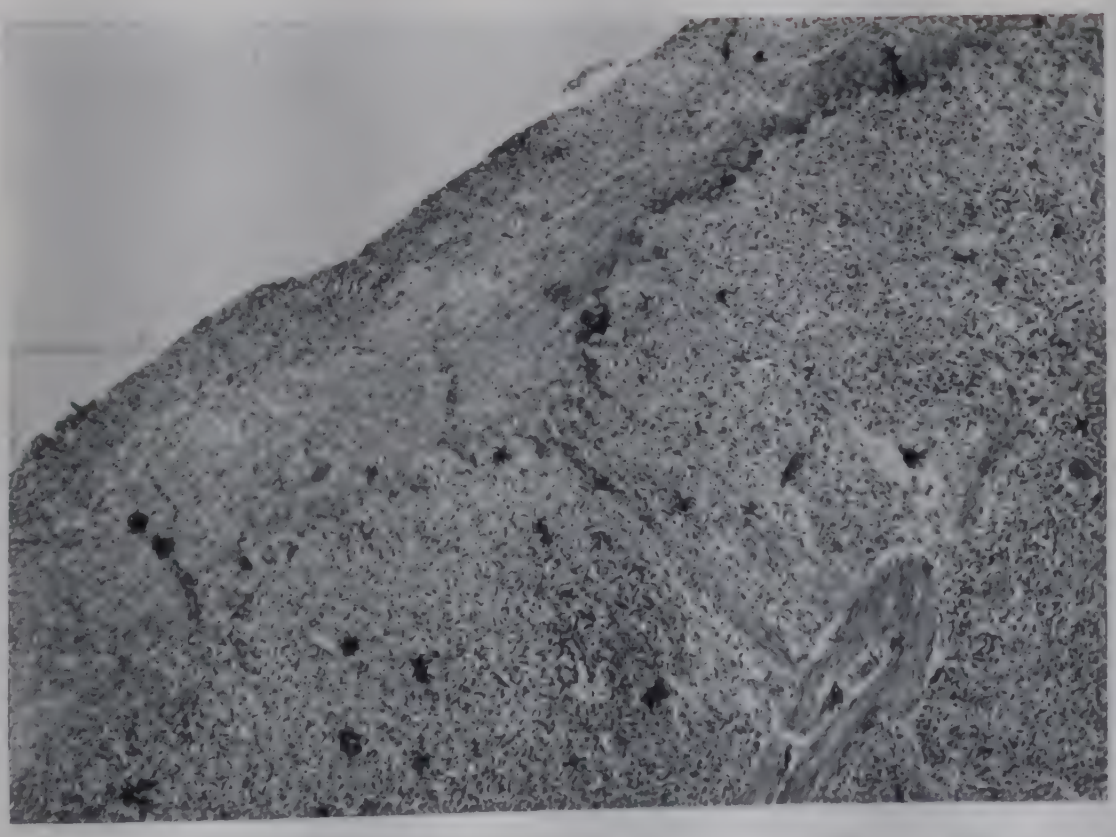


FIG. 20. Photomicrograph of an implanted spleen after 19 days. Digestion had occurred to the level of the gastric stoma. A thin zone of acute inflammatory reaction, hyalinization, and necrosis overlies the splenic parenchyma which retains its structural characteristics. (Courtesy, Price and Lee: *Surg., Gynec. & Obst.*, **83**:61.)

Intestine

Serosa

Two techniques have been employed in studying the effects of gastric secretions on the serosal surface of the intestine; (a) a free loop of bowel is sutured into an opening in the stomach, so that more or less of the serosal surface of the loop is inside the stomach and enough of the mesenteric border is spared to insure the integrity of the circulation, or (b) a segment of intestine with its blood vessels is isolated and converted into a closed loop by purse-stringing the ends; this loop is then implanted into the stomach as in the first method, and the continuity of the remaining intestine restored by an anastomosis. Since the underlying principle of the two methods is the same, no reference will be made in the following discussion to the particular method used by the various investigators. Although the closed loop should be more susceptible, because it should become distended with secretions which would interfere with the blood flow of the intestinal wall, it cannot be determined from the various reports whether this actually occurred.

Contejean (10), who first investigated the fate of intestinal loops implanted into the stomach, showed that if a sufficiently long period of time is allowed (about two weeks), the gastric juice will erode all of the coats of the bowel from the exposed serosa inward and create a gastroenterostomy. This observation was confirmed by Kathe (21), Best (7), Kawamura (24), Katzenstein (22), Dragstedt and Vaughn (14) and Price and Lee (37); it was denied, on the other hand, by Hotz (20), Fiori (16), Marie and Villandre (30), and Licini (26). All of these investigations appear to be above criticism from the standpoint of attention to the preservation of the blood supply. Licini (26), in particular, devised a technique which would be certain not to impair the circulation in any part of the implant in contact with the gastric juice, as might be the case when sutures are placed through the bowel at the edges of the opening into the stomach. He made a lesion on the anterior wall of the stomach by cautery, without penetrating the mucosal layer; against this cauterized area the organ under study was placed and fixed by sutures at some distance from the edge of the lesion. Two or three days later the mucosa eroded through and the organ was exposed to gastric juice. The fact that none of the organs studied by Licini was affected might indicate that the opening in the stomach was made sufficiently small, or was sufficiently reduced by contraction of the gastric musculature, to allow the exposed surface to be covered by epithelium in a relatively short time. Indeed, the author's studies show that the latter actually took place, but he did not relate it to the size of the

exposed surface. Katzenstein (22, 23) believed that the susceptibility of the gastrointestinal serosa to attack by gastric juice follows a gradient; according to his findings the jejunum is readily digested whereas there is no effect on the stomach or duodenum. However, we know from observations on Mann-Williamson dogs that the duodenal serosa is susceptible to digestion by the gastric juice, because in these dogs a jejunal ulcer will occasionally perforate into the duodenum; in fact, whenever a Mann-Williamson dog with all the signs of advanced jejunal ulcer recovers spontaneously, a diagnosis of perforation into the duodenum is fairly certain. Moreover, spontaneous gastroduodenostomy has been reported (44, 49) in man.

Intestinal Mucosa

When we review the reports on the exposure of the intestinal mucosa to the gastric juice, we find the results less divergent and the contradictory observations more easily reconciled. The three principal methods of experimentation on this problem will be considered separately.

Side-to-side Anastomosis of the Stomach to an Isolated Intestinal Loop

This procedure amounts to a gastroenterostomy without direct access of the alkaline duodenal contents to the anastomotic site (Fig. 21). Preliminary work by Otte (34) indicated that the mucosa of an isolated loop of intestine was not attacked by artificial gastric juice, but the observation period was probably much too short. With anastomosis of the stomach to an isolated segment of jejunum in five dogs, Katzenstein obtained almost complete digestion of the intestinal mucosa within two or three days. This was denied by Hotz (20), who used the ileum and observed his dogs up to 40 days, by Best (7), and by Dogliotti and Riccio (12).

The most comprehensive work on this phase of the problem was that reported by Gallagher (18). Of 17 dogs with a jejunal segment (loop) anastomosed to various parts of the stomach, ulceration was noted in only two instances; these ulcers occurred in the ends of the intestinal segment, where there was much scar tissue and stasis of stomach contents. Seven other dogs with similar operations were given 200 cc. of 0.22 to 0.62 per cent HCl once or twice daily by stomach tube; in five of these dogs the implanted loop had been traumatized by the deliberate application of a clamp at the time of operation. During an observation period extending to 154 days, ulceration of the intestine was found in one dog, with the same characteristic location as in the previous two cases. It is apparent from these results that ulcer occurred only occasionally, and in that part of the intestine where (a) the circulation was poor as a result of the presence of scar tissue, and (b) there was a predisposition to stasis

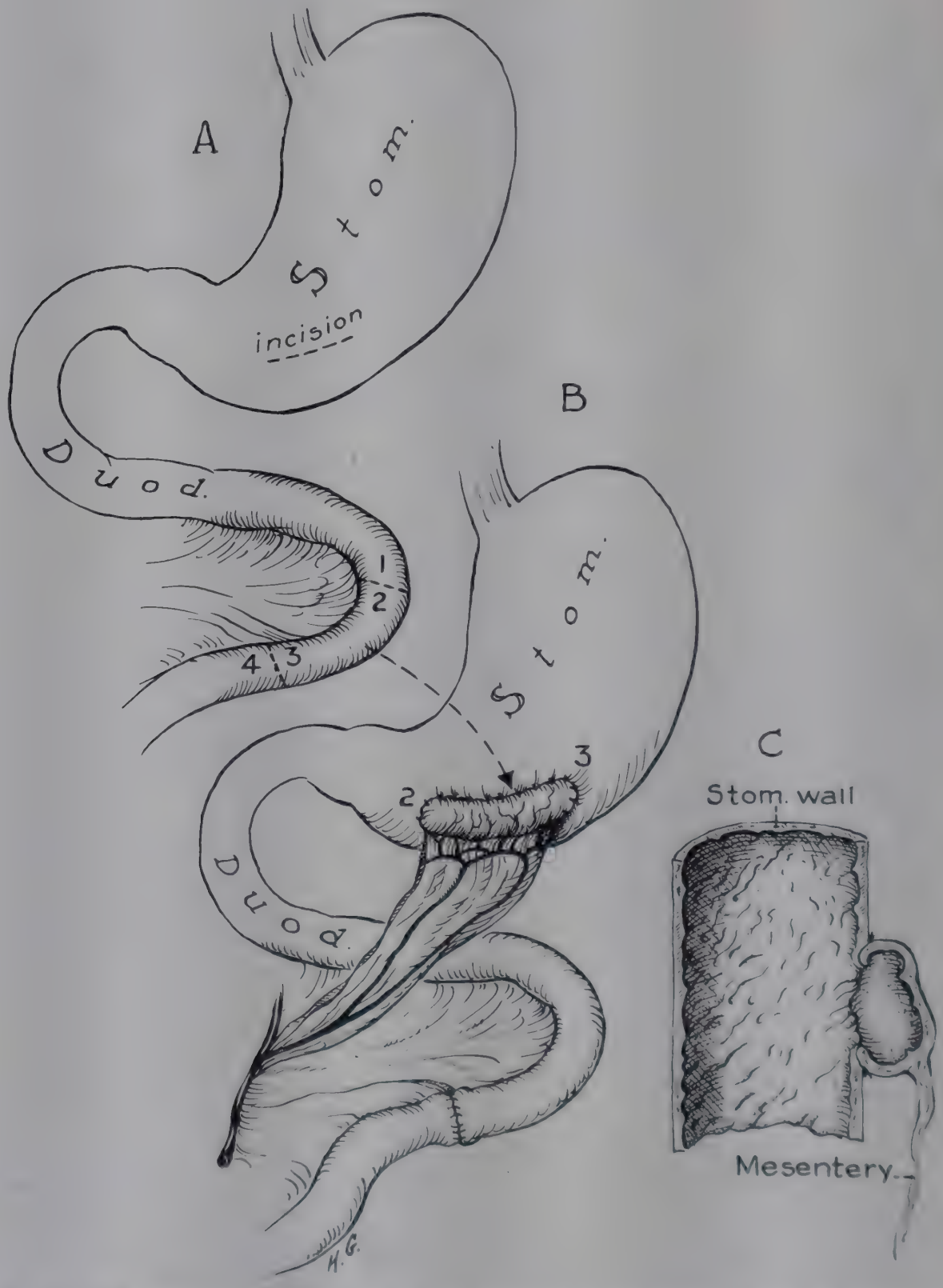


FIG. 21. Side-to-side anastomosis of the stomach to an isolated loop of jejunum.

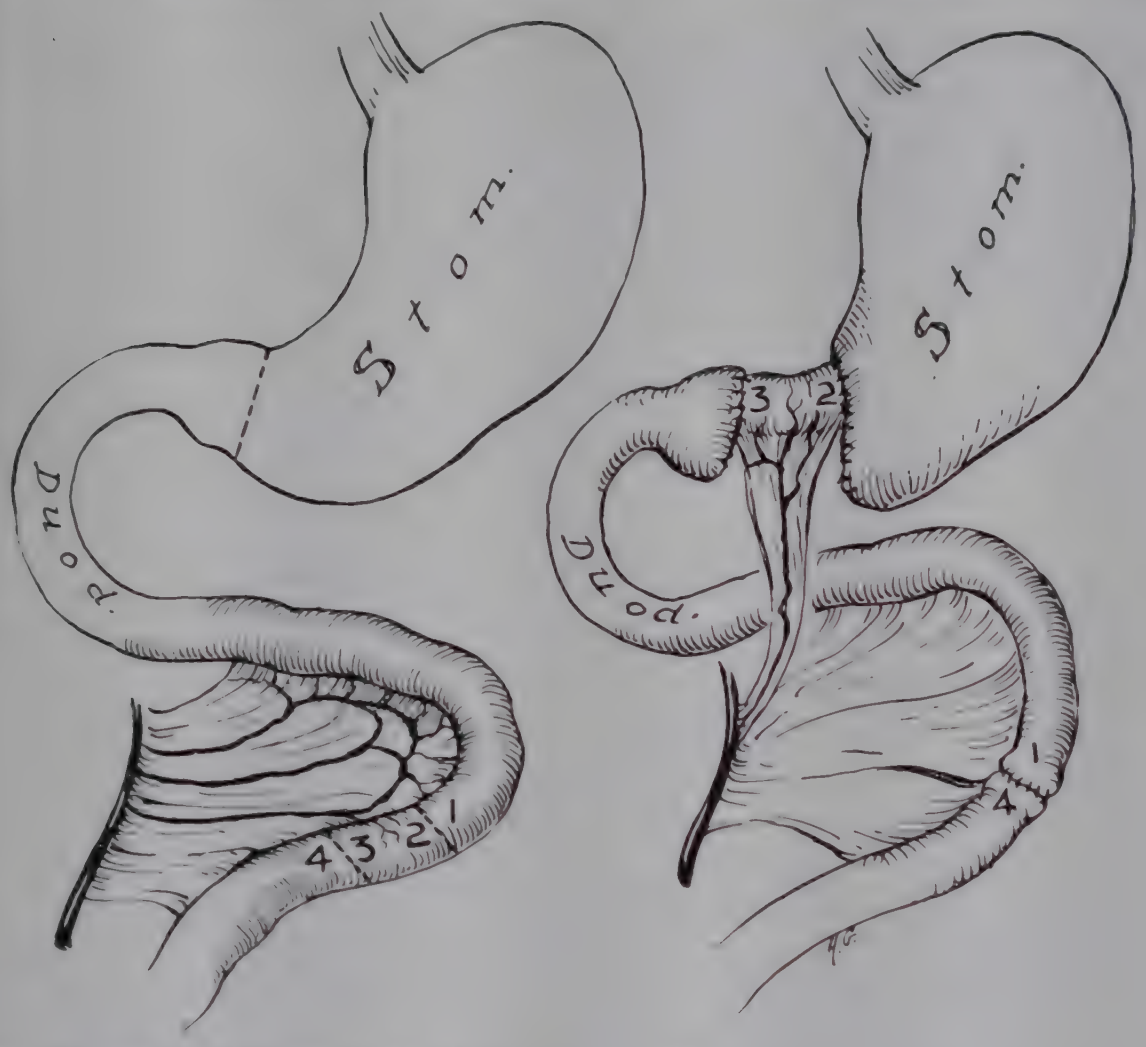


FIG. 22. Tubular insertion of a short segment of upper jejunum between the two ends of the divided pyloric antrum.

of the food and gastric juice. Artificial hyperacidity and operative trauma failed to increase the incidence of ulcer in the stomach, the implanted intestine, or the ends of the implant. How effectively the acidity in contact with the mucosa of the loop was actually raised is questionable in the absence of specific data, since it is likely that the amount of acid introduced was rapidly buffered.

Under this group of experiments may be mentioned the work of Fiori (17), who divided the pyloric antrum and anastomosed a segment of jejunum, sleeve-fashion, into the stomach (Fig. 22). His three dogs lived 5, 22, and 43 days respectively, and in no case was the intestinal wall affected. A longer observation period would have been desirable.

Patch Implants of the Intestine into the Wall of the Stomach

In this technique, a small segment of intestine is isolated and opened in its long axis, so as to form a patch, which is then sutured into a window in the stomach (Fig. 23). Obviously, such experiments are significant only when an adequate blood supply to the patch is assured. This depends at

first on preserving a pedicle, but the work of Price and Lee (37) has shown that eventually the implant acquires a sufficient blood supply from the adjacent stomach wall to permit severing the pedicle.

Marie and Villandre (30) apparently were the first to make patch implants of the intestinal mucosa to the stomach. In none of the three preparations observed by them was any change in the implant noted. Further-

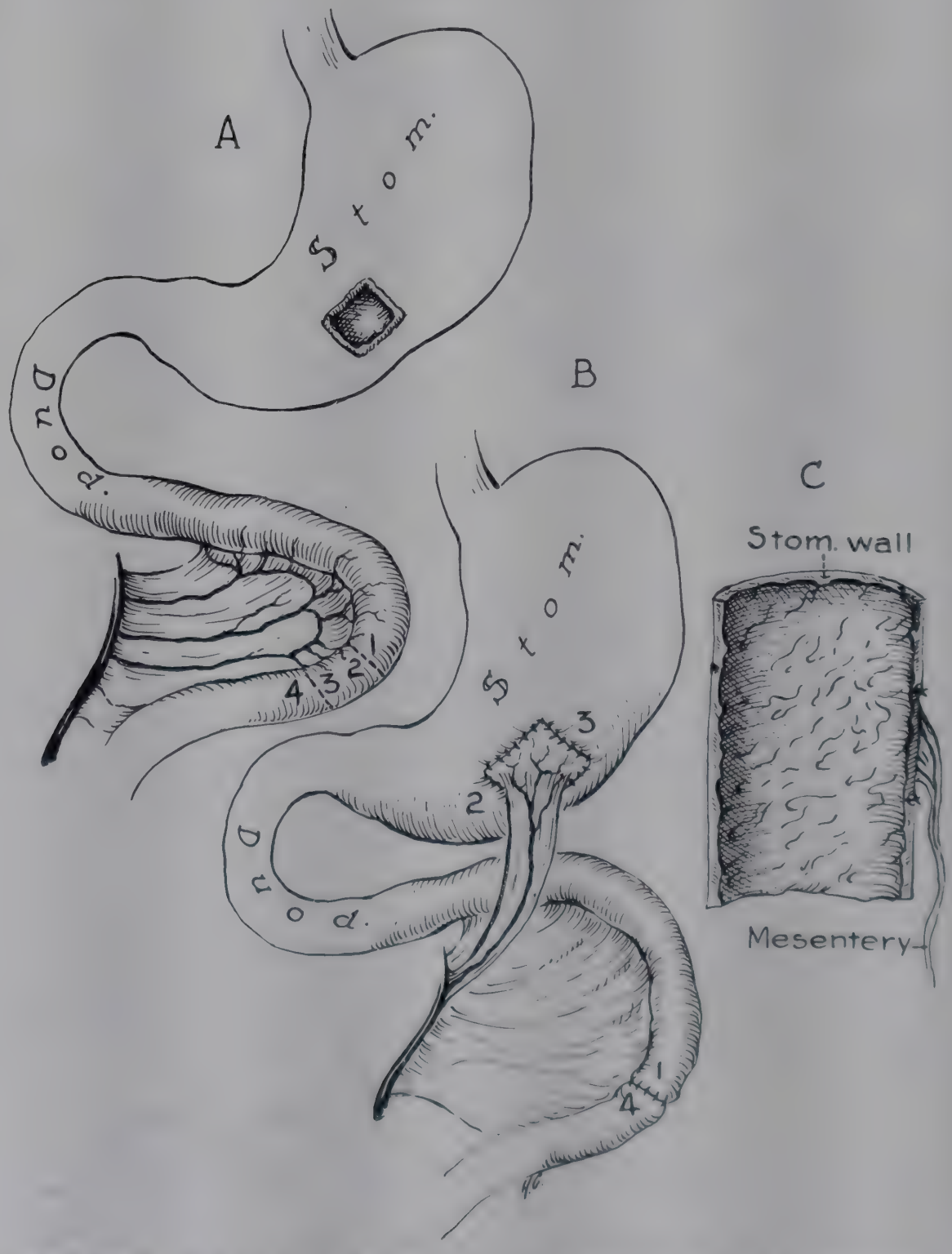


FIG. 23. A patch implant of jejunum into the anterior wall of the stomach.

more, from one implant examined at laparotomy after five months, the authors removed a section of the mucosa, leaving a thin translucent layer of muscularis and serosa; 30 days later this was found completely healed. Mann (29) placed jejunal patch implants on the posterior wall of the pyloric antrum in 14 dogs; the animals were examined from the second to the three hundred thirtieth postoperative day, and the only instance of ulceration was at the site of a retained silk suture. The author concluded that gastric juice was probably not the primary cause of jejunal ulcer—a decision which he later had cause to reverse, interestingly enough, when he devised another technique of bringing the stomach contents to bear on the jejeunum.

De Takats and Mann (11) placed jejunal patches saddle-wise over the lesser curvature of the stomach in 25 dogs; ulceration of the patch occurred in three instances, and the authors thought that the frequency of ulcer would have been greater had it been technically possible to place the implants at exactly the desired site directly over the lesser curvature. They believed that mechanical stress was therefore a definite factor in the production of jejunal ulcer. The stretch on the veins in the pedicle may have caused passive congestion of the mucosa of the implant in their experiments; at any rate Morton (31, 32) prepared 13 dogs with jejunal patches on the lesser curvature near the pylorus and observed ulceration in only one dog after 163 days. A Mann-Williamson operation was then performed on five of these dogs, and the jejunal patch became ulcerated in three instances. In eight dogs with jejunal patches implanted into the stomach elsewhere than on the lesser curvature, the Mann-Williamson operation did not lead to ulceration of the patches although typical ulcers developed in the jejunum near the gastrojejunostomy.

Reerink (38) found that patch implants of the colon do not ulcerate, and, according to Dragstedt and Vaughn (14), patch implants of the duodenum, jejunum, ileum, and colon may be exposed to the gastric contents indefinitely without harm to the mucosa of the bowel; their observation period extended to 12 months.

The only conflicting opinion concerning the fate of patch implants into the stomach came from Palma (35), who claimed to have observed ulcers in seven of nine patches transplanted to the pyloric antrum, whereas no ulceration occurred in nine transplants to the fundus. We may question the accuracy of these observations because in the same paper the author called attention to two cases of spontaneous duodenal ulcer, which, from the photographs shown, were certainly either mucosal depressions or Peyer's patches.

Price and Lee (37) noted that when a jejunal implant is converted to a transplant by division of the pedicle, the transplant continues unmolested

by the gastric contents. But if the transplant is invaginated into the stomach, it is digested, while the adjacent mucosa of the stomach remains normal. This is a striking illustration of the difference between a tangential implant and an implant into the lumen of the stomach.

Patch Implants of the Intestine into an Isolated Pouch of the Stomach

Andrus and his associates (3) implanted a patch of jejunum into the wall of an isolated gastric pouch (Heidenhain or Pavlov) in dogs. They did not report whether an ulcer developed in the patch, but reported that the erosion of the skin about the pouch healed, which they interpreted as indicating that the secretion of the pouch was diminished. We (19) implanted jejunal patches (Fig. 24) into a pouch of the entire stomach in two dogs and into one Heidenhain and one Pavlov pouch. The secretion of the pouches was in no case affected by the implants and the implants did not develop ulcers. Similar results were obtained by Kolouch, Dubus and Wangensteen (25). In these experiments, the secretion of the pouches was continuously draining to the outside. If gastric pouches, prepared with intestinal patch implants, were to be obstructed to prevent the free drainage of the acid-pepsin, it is probable that the implants would ulcerate; this experiment has not, to our knowledge, been performed. In an approach which is not strictly analogous, Kolouch et al. (25) found that when animals with jejunal implants in the gastric wall were subjected to the continuous action of histamine (histamine in beeswax), ulcers developed in the patch in all cases. Also, Goldberg (45) reported that when a short ileal loop is used to make a fistula into the fundus of the stomach, the mucosa of the loop rarely ulcerates; but when a portion of the fundus is made into a pouch, so that the intestinal loop drains the gastric juice, ulcers frequently occur in the intestinal segment.

Effects of Jejunal Patch Implants into the Stomach on Gastric Secretion and on the Occurrence of Experimental Ulcer

In a recent series of papers, Andrus, Lord and Stefko (2, 3, 4, 5, 27, 28, 41) have reported that the implantation of a pedicled graft of jejunum into the wall of the stomach produces profound effects on gastric secretion. According to their observations, a jejunal pedicle graft implanted in the gastric wall tends to lower the fasting acidity and to reverse the response to histamine injection; that is, administration of histamine to a dog with a jejunal implant in the gastric wall is claimed to depress rather than increase gastric acidity. The stimulating effect of alcohol on gastric secretion is also reported to be abolished or greatly reduced by these jejunal implants. Ileal and colonic transplants into the stomach wall are stated to be



FIG. 24. Showing a patch of jejunum which had been exposed to gastric contents for four months. The mucosa of the patch is healthy. Though a few small hemorrhagic areas may sometimes be seen in such implants, we have never found ulcers to be present.

ineffective, whereas jejunal transplants are somewhat more effective than duodenal transplants.

The mechanism of inhibition of gastric secretion by jejunal implants has been postulated to be due to a substance formed by the jejunal mucosa which, when it bathes the gastric mucosa, depresses acid secretion. Thus, saline washings of Thiry loops of jejunum when placed in the stomach of a normal dog and permitted to remain for 10 minutes are reported to prevent, or greatly diminish, the gastric secretory response to histamine injection.

Pedicle grafts of jejunum are claimed to be effective both in the prevention and in the cure of experimental ulcers produced in dogs by the prolonged administration of histamine in beeswax. The operation has been performed by Andrus and his associates in patients with duodenal or marginal ulcer, with favorable immediate clinical results.

In our hands (19), neither perfusion of stomach pouches with jejunal washings nor implantation of pedicled jejunal grafts into the stomach *in situ* had any noteworthy effect on the gastric secretory response to histamine stimulation. Andersen and his group (1) studied seven dogs before and after implantation of jejunal grafts into the stomach and were unable to detect any significant alteration in the gastric secretory response to the Wilhelmj-O'Brien beef extract test-meal. Similar results have been obtained by Kolouch and his colleagues (25), who found also that the continuous action of histamine (histamine in beeswax) in these animals resulted in ulceration of the jejunal patch in each instance. Finally, Saltzstein and Kurtz (40) reported that jejunal patch implants into the stomach did not prevent or even delay the appearance of jejunal ulcers in Mann-Williamson dogs. It is interesting that, in one of their dogs, the implanted patch was ulcerated.

Thus there has not been reported, to our knowledge, any confirmation of the extensive experimental work of Andrus et al. on the supposed effect of jejunal implants into the stomach on gastric secretion.

The experiment which Saltzstein and Kurtz (40) performed as a test of the validity of Andrus' hypothesis had been performed earlier by Morton (31) for a different purpose. Although the results lend no support to Andrus' views, they do illustrate strikingly another significant point. In this experiment two pieces of jejunal mucosa are exposed to the gastric contents; namely, the implant and the segment of jejunum at the gastroenterostomy. The fact that the latter is the one which consistently ulcerates indicates that special factors operate at the stoma. Among the factors to be considered are (1) the nozzle effect of the stoma, (2) the exposure of the jejunal mucosa at the stoma to all of the gastric juice (both the quantity and the concentration of the acid to which the mucosa is exposed are factors in producing exhaustion of protective functions), and (3) spasm of the

jejunal musculature. Since ulcers occur when the jejunal musculature is removed, the spasm factor is not important (see p. 354).

Other Tissues

Omentum

Several investigators (42, 15, 36) have shown that an opening through all the layers of the gastric wall may be repaired successfully by suturing a piece of omentum over the defect; indeed, this principle has long enjoyed clinical use in the surgical repair of perforating ulcers (9). That this fact is not contradictory to the finding of Bocci (8), mentioned previously, was proved recently by Price and Lee (37). They demonstrated that when holes in the stomach wall were covered with patches of omentum, granulation tissue formed, and the area was covered by ingrowing epithelium. But when a large tongue of omentum with intact blood supply was placed inside the stomach it was digested down to the point of entrance.

Other Organs and Tissues

According to earlier reports, the urinary bladder (7) was digested when implanted into the stomach, but pancreas (26, 39) and kidney (14) were not. However, Price and Lee (37), in extensive experiments, proved that normal gastric juice digests all living tissue except the mucous membrane of the stomach. They noted that the susceptibility of the various living tissues was generally as follows:

1. Seromuscular coats of the intestine and gallbladder (most susceptible).
2. Omentum and cartilage.
3. Kidney, spleen, lung, liver, pancreas.
4. Fibrous connective tissue, skin.

A very significant experiment was that in which a rectangular patch of the stomach wall was turned into the lumen. When the mucosa of the resulting flap everted itself in such a manner as to protect the underlying layers of the flap from the action of the gastric juice, no digestion resulted; the flap in such an instance remained indefinitely as a polyp-like process extending into the cavity of the stomach. Only when the submucosal tissues of the flap were first attacked by the gastric juice, and the mucosa thereby deprived of its blood supply, did complete digestion occur.

Implants into the Intestine

There has been very little investigation of this aspect of the problem. In 1911, Rosenbach (6) implanted the tail of the pancreas into the duodenum in 9 dogs, and into the jejunum in one dog. The period of observation was

limited to 16 days; and, although destructive changes were present in the implanted segment of pancreas in all cases, the author concluded that the organ resists tryptic digestion.

In a more recent report by Necheles, Ling, and Fernando (33), the authors stated under "Technique" that they implanted "a lobe of the liver, the upper pole of a kidney and pieces of omentum into the intestine" in dogs. However, in their discussion of the results, no mention is made of the fate of the liver or kidney. Omental implants were made by drawing a tip of omentum into the intestine for a distance of 4 cm. The dogs were observed up to 73 days after the implantation; of a total of 58 experiments, there were only 8 instances of marked diminution or disappearance of the implant, and in these cases there may have been an embarrassment of the blood supply of the omental tag.

Discussion

The work of Price and Lee (37) shows that *under certain conditions* the mucous membrane of the *normal* stomach manifests a unique immunity to the digestive action of gastric juice.

The sequence of events following the implantation of a considerable segment of an organ or tissue into the cavity of the stomach suggests that the stomach proceeds to whittle the intruding tissue down flush and then tries to cover it over with epithelium. If the area of the resulting lesion is not too great, say not more than 2 or 3 cm. in diameter, the probability is that it will be epithelialized. If it is greater, it would be unlikely ever to heal, just as in the case of large excision ulcers or old chronic ulcers which, even after maximum contraction, leave a greater denuded surface than the regenerating epithelium can cover. In the latter case, there remains a scar which may subsequently break down, as indeed Price and Lee observed in those experiments in which they removed extensive areas of gastric mucosa.

It appears then that the procedure of implanting living tissue *into the cavity* of the stomach has a significance materially different from that in which the tissue is simply placed against an opening in the stomach wall. The former approach is rather analogous to experiments in which exposed mucosa is subjected artifically to the prolonged action of acid or acid-pepsin, as has been discussed by us in a recent paper (50). It was shown that there is a gradient of susceptibility in the mucosa of the gastrointestinal tract; and it is likely that, if the same technique were applied to other exposed tissues, the gradient would prove to follow the order observed by Price and Lee. But when living tissues are made a part of the stomach wall, i.e. implanted tangentially, the experiment is no longer merely a test of susceptibility, because there is introduced the factor of the remarkable

ability of alimentary epithelium to preserve or restore its continuity. So, in a tangential implant of a parenchymatous organ into the normal stomach, the test of susceptibility is invalidated by the fact that the stomach strives to *protect* the implant from gastric juice—partly by the secretion of mucus, but mainly by growth of epithelium over the exposed area.

Support for this view is seen in (1) the experiments on implantation of an intact loop of intestine, and (2) the implantation of spleen into an obstructed pouch of the stomach. According to Price and Lee, the seromuscular covering of the intestine had the highest susceptibility of all the tissues tested. But taking all the evidence together, it appears more likely that this merely exemplifies the principle of restoration of surface continuity in the digestive mucosa. It will be recalled that in the experiments of Licini (26), the implanted serosal surface of the intestine was not eroded through by gastric juice. This was because the opening in the stomach wall was small enough for the gastric epithelium to restore continuity by growing over the implant. When, however, the area of implanted serosal surface was much greater, it was eroded through before gastric epithelium could cover it, consequently mucosal continuity was established by the alternate method, i.e., spontaneous gastroenterostomy. In the case of solid organs, as kidney and spleen, there is no such alternative; but because of the thickness of the organ, time is available for the epithelium to cover the exposed surface, whereas in the same length of time the hollow gallbladder or intestine are broken through completely if the area exposed is large. Or, if a factor is introduced which prevents the gastric epithelium from regenerating, the parenchymatous tissue will be progressively digested, as was shown by Dragstedt and Vaughn. In their experiment, the spleen was implanted into a stomach pouch, and the pouch was then plugged to prevent drainage of the juice. In the presence of retained acid unbuffered by food, the epithelium was unable to establish a secure foothold on the exposed pulp of spleen. Similarly, Price and Lee (46) showed that when histamine in beeswax was injected subcutaneously in dogs with organs implanted into the stomach, the digestion of the organs was in all cases accelerated and intensified.

The susceptibility of the omentum to the action of digestive enzymes has long been known, e.g., from observation of fat necrosis in pancreatic disease; the erosion of skin and connective tissue by digestive ferments is also a well-established phenomenon, and in fact is not infrequently a troublesome clinical problem. So, the importance of Price and Lee's work lies in the demonstration that living parenchymatous organs too are digested by *normal* gastric contents, whereas the normal gastric mucosa is immune. This fact permits one to conclude, for instance, that the penetration of a peptic ulcer into adjacent seromuscular or parenchymatous tissue is not *per se* an indication of abnormal gastric secretion.

In regard to any organ-implantation experiments into the stomach, the question always remains to what extent the blood supply of the organ may be compromised by contraction of the stomach musculature. This objection could be ruled out by performing experiments in which gastric juice is brought to bear on the various parenchymatous organs *in situ*.* If the susceptibility of these tissues to normal gastric juice should be thus confirmed, a series of implantation experiments into the intestine, i.e., an extension of the work of Necheles et al., would be desirable; for, as we indicated in Chapter 2, the alkalinity of the intestinal secretions is so relatively slight that one would not expect tissues to be as susceptible to damage by these secretions as by those of the stomach.

Summary

It has been well established that when the mucosa of the intestine is made a part of the internal stomach wall either by patch implants or by lateral anastomosis of the stomach to a segment of intestine, ulceration of the intestinal mucosa rarely follows. The numerous jejunal implantation operations performed by Andrus and co-workers and by the several groups who have attempted to confirm their findings add overwhelming evidence of the ability of the jejunal mucosa to withstand exposure to normal gastric contents.

On the surface, the evidence seems to indicate that a marked elevation of acidity, or a concentrated action of acid, or both, will cause ulcer to develop in jejunal patch implants. However, the picture is not clear enough to permit a final unequivocal conclusion. The observations bearing on the question are as follows:

1. Ulceration did not occur in implants made into stomach pouches of various types, although in these preparations the intestinal mucosa is subjected to the action of acid unbuffered by food or duodenal secretions.

2. Ulceration occurred in only one of seven dogs in which implantation of a jejunal patch *into the body of the stomach* was followed by a Mann-Williamson operation, although five of these dogs developed jejunal ulcers at the site of the gastrojejunostomy. It will be recalled that most Mann-Williamson dogs manifest a prolonged gastric secretory response to a test-meal. Thus it is clear that in these experiments the mucosa of the implant

* Gaglio (47) performed an experiment based on the same principle. He diverted the urine from the bladder via external ureteral fistulae and ligated the urethra. He then placed artificial gastric juice in the bladder, and after five hours noted hyperemia, scattered ecchymoses, and superficial ulceration of the mucosa. Langenskiold (48) introduced natural canine gastric juice (0.53% free HCl) into the urinary bladder through one of the ureteral openings and allowed it to flow out through a cannula placed in the urethra. After one hour of perfusion he observed advanced digestion of the bladder mucosa.

exhibited a resistance while the jejunal mucosa at the stoma was ulcerated. This may be explained by pointing out that only a portion of the acid gastric contents bathed the implant while all had to pass over and bathe the jejunal mucosa in the region of the stoma. This may exhaust the protective mechanism in the cells of the jejunum in the region of the stoma. A mechanical nozzle effect may also be concerned.

3. Ulceration occurred after the Mann-Williamson operation in three of the five jejunal patches which had previously remained unharmed *on the lesser curvature near the pylorus* for some five months. The significance of these findings is open to question because of the possibility of impaired blood supply to the implant resulting from the Mann-Williamson procedure. De Takats and Mann commented on the technical difficulties of placing a pedicled jejunal implant on the lesser curvature of the antrum. The work of Morton deserves to be repeated; it would be well to have the implant in place long enough to make it independent of the blood supply from the pedicle, so that there would be less likelihood of introducing the possibility of vascular impairment at the time of the Mann-Williamson operation.

4. Ulceration of the implant occurred consistently following the administration of histamine in beeswax. But in these circumstances the gastric mucosa may also develop ulcers; thus the effect of the hyperacidity cannot be regarded as specific for the mucosa of the implant.

All tissues other than the intestinal mucosa appear to be subject to digestion by gastric juice secreted in ordinary amounts and concentrations; however, this cannot be regarded as entirely settled. Similarly, the fate of living tissue exposed to the digestive action of the upper intestinal contents remains to be determined.

Nevertheless, it is clear that impairment of the blood supply of the mucosa renders its digestion possible by gastric juice secreted in ordinary amounts and concentrations.

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CHAPTER 6

Healing of Acute and Chronic Ulcers

Introduction

When Pavy (34), in 1863, removed a piece of mucous membrane from the stomach of a dog and found that the defect was completely healed in 10 days, he achieved the distinction of publishing the first, and almost the only, experiment in the field of gastric ulcer which everyone has been able to confirm. Within a comparatively short time (1875), Quincke (37) reported that he had produced gastric lesions by pinching off pieces of mucosa with a forceps, by ligating a piece of mucosa with thread, by direct excision of the mucosa by cauterizations with a hot iron, by surface application of alcohol, silver nitrate, or fuming nitric acid, or by submucosal injection of silver nitrate or ferric chloride solutions; all of these lesions were reported to heal by the twenty-first day by a process consisting essentially of granulation of the base of the defect and ingrowth of epithelium from the edges. In the following year, Leube (73) passed a stomach sound in a patient and accidentally, during gastric lavage, stripped off a piece of mucosa approximately 3 cm. long and 3 mm. in width. The patient died some four months later, and an autopsy showed no trace of ulceration or scarring in any part of the stomach. Similar observations were recorded by others (48, 49, 50), thus providing unique clinical confirmation of the experimental findings.

Cohnheim (7) produced acute lesions of the stomach in dogs and rabbits by corrosion, burning, bruising, or wounding; he was the first to stress the fact that the real problem is not to produce acute lesions, but to account for the fact that in the human such lesions often become chronic. However, it was many years before numerous investigators abandoned the impression that if acute lesions could be produced by any method, chronicity was guaranteed by the action of the gastric juice; and in certain instances this erroneous viewpoint persists even today.

Since it is evident that defects of the mucosa and wall of the stomach and intestine are usually repaired rapidly, and since the mechanism of this repair is basic to the problem of peptic ulcer, a general consideration of the biology of wound healing is appropriate here.

Biology of Wound Healing

Most of the biologic studies on wound healing treat of skin wounds. Arey (92) states that internal wounds of the serous and mucous surfaces differ in no fundamental way from those of the external surface. This being the case, it should be profitable to review first the healing of skin wounds, since such knowledge should cast some light on the healing of ulcers of the stomach, duodenum, and jejunum. The following summary of the processes concerned in the healing of wounds is based on Arey's (92) review of that subject.

Healing of an Acute Ulcer of the Skin

The Latent Period

Fibrin is deposited when active bleeding ceases. It covers the surface and fills the exposed tissue spaces and the open vessels. Connective tissue and endothelial cells are proliferating actively by the second day, sometimes within one or two hours. Capillary buds appear and granulation tissue covers the denuded surface in six to eight days. Each granule or hillock of granulation tissue consists of a core of capillaries surrounded by fibroblasts and wandering cells. Thus, the wound is covered by a cellular protective membrane which before consisted only of fibrin. The cellular layer has a lower permeability than the fibrin, as indicated by the observation that the application of alcohol is less likely to cause pain when granulation tissue rather than fibrin covers the wound. The granulation tissue serves as a defense against infection because it is very vascular, secretes actively when irritated, manifests a local leukocytosis, and presents a barrier of closely packed, vigorous cells. In the absence of irritation the secretion of healthy granulation tissue is scanty, mucoid, and contains relatively few leukocytes.

Fibroplasia performs the following functions: (a) Restoration of lost connective tissue (reparative fibroplasia), (b) replacement of other lost tissue elements which cannot regenerate or which regenerate poorly (replacement fibroplasia), (c) protection of wound surface, and (d) *provision of a type of floor for the wound over which the epithelium can migrate.* When an epithelial defect occurs which extends only into tissue onto which epithelial cells can migrate immediately, no significant fibroplasia occurs (e.g., the erosion).

Active Contraction

From two to five days after an acute ulcer of the skin larger than 1.5 cm. is made, the wound starts to decrease in size by a process of contrac-

tion. This contraction, which pulls the edges of intact skin together to the extent of its elasticity, is believed to be due to a contraction of connective tissue. It occurs to a remarkable extent in mobile skin and is hardly perceptible in fixed skin. The rate of contraction is directly proportional to the size, and not to the age, of the wound; thus wounds of various sizes tend to equalize as healing progresses. The contraction ceases when the wound is no larger than 1.0 to 1.5 cm. in diameter. This phenomenon, which is essential for the healing of larger cutaneous ulcers, has little significance in the healing of wounds of 1.5 cm. or less in diameter.

Epithelization

Wounds Larger Than 1.5 Cm. in Diameter. Immediately after the trauma, mitosis subsides or disappears for a variable period. Mitosis then reappears within a day or two among the basal and columnar cells of the Malpighian layer. As granulation tissue forms and contraction starts, the newly formed epithelial cells creep out over the granulation tissue by amebism. Mitosis continues in the original margin as contraction progresses, but not in the outgrowing cells until several days after they have become firmly fixed in place; then the new cells formed in the mitotic areas creep out. The larger and deeper the wound, the greater the mitosis at the margin of the original wound. The larger the wound, the more dependent is the completion of epithelization on mitosis in the new epithelial covering.

At first, there is no union between the ameboid epithelial cells and the underlying fibrin fibers or granulation tissue. It is believed that the fibrin fibers are important in the stereotropic response of the epithelial cells, or the manner in which they creep along the floor of the ulcer. It is believed that a sticky substance on this surface causes agglutination to fibrin fibers or to the mucoid secretion of the fibroblasts covering the granulations; at any rate, until the outgrowing epithelium becomes firmly adherent to the substrate, the advancing cells are easily washed off. When the epithelial cells become agglutinated, the granulation tissue beneath becomes restrained and an areolar tissue forms, beneath which connective tissue fibrils start to condense. The regeneration of the epithelium is never complete; hair follicles and sweat and sebaceous glands do not regenerate.

Contraction and Epithelization Are Interdependent. Epithelization follows and continues with contraction, and usually in the skin but not necessarily in the alimentary tract, brings the contraction to an end. Epithelization ceases after contraction has ceased if the area remaining to be covered is greater than 2.5 cm. "In large wounds the growth force of the regenerating tissue may exhaust itself so that an ulcer develops in the midst of torpid scar tissue" (Arey).

Wounds Less Than 1.5 Cm. in Diameter. In skin wounds less than 1.5 cm. across the cells start to migrate early and before contraction starts. When the base of the defect is such that it can receive migrating epithelial cells immediately (the erosion), the young cells already present begin to migrate at once. Then, the denuded surface is covered quickly (6 to 10 hours) and mitosis starts to replace the deficit created by the migrated cells.

Cicatrization

Cicatrization is the process of formation of a scar. A scar is the newly formed tissue present after the healing of an injury which has peculiarities distinguishing it from the normal tissue. In the case of the skin it is the newly formed connective tissue covered by the newly formed epithelium.

Before Complete Closure. Cicatrization starts in the edges of the ulcer before the ulcer is closed. Fibrils appear in the granulation tissue. They represent a gelation either of a secretion of fibroblasts or of fibrinogen from the blood plasma; the question is unsettled. The fibrils undergo further condensation to form white connective tissue fibers. The newly formed connective tissue or scar is rich in blood vessels; even when covered with epithelium it is red and is called a red scar. As the young connective tissue fibers further condense and contract the blood vessels disappear and the scar becomes white.

In delayed healing or in large ulcers, the contraction of connective tissue at the margins produces radiating or stellate ridges about the ulcer. In some cases, by the time the ulcer is closed the deformity is marked.

After Closure. Cicatrization continues for an extended period after complete epithelization of the wound. In the case of a small ulcer, the size of the permanent scar remains the same or smaller than the original ulcer. In many cases, particularly in large ulcers or wounds, the scar enlarges and becomes less thick and more pliable with time. This is particularly true when the skin involved is mobile.

The pH of Granulation Tissue

The pH of healthy granulations as determined by the best methods yields values ranging from 5.8 and 7.7; the more acid values are found under noninfected scabs. In the presence of most infections, and when the CO_2 is permitted to volatilize, the pH is higher. An increase in acidity up to pH 4.5 causes capillary dilation; with a further increase, pH 4.2 for example, the capillaries constrict.

Relation of Acidity and Potassium to Pain in the Skin

Phosphate buffer solutions of different degrees of acidity have been injected into the skin. Pain occurs at a pH of 7.2 and becomes very severe

at a pH of 5.9. Pain does not arise from an acidity of pH 5.8 under scabs because pain nerves are absent. Pain nerves grow into scars in the epithelium of the skin late and in relatively few numbers. The injection of potassium chloride is very painful; this is significant in view of the fact that injured or inflamed cells release potassium. Histamine released locally in inflammation may decrease the pain threshold (93).

Factors Which Influence the Healing of Skin Wounds

Irritation

A nonirritating dressing delays contraction and, hence, healing. Mild irritation speeds contraction and facilitates healing, apparently by increasing the rate of formation of fibrils and their condensation into white fibrous connective tissue. Irritation just short of destruction produces exuberant granulation or "proud flesh," or excessive fibroplasia. Excessive irritation or infection delays contraction chiefly because fibroblasts are destroyed. Epithelial cells will not enter a necrotic area of granulation tissue; they creep over only healthy granulation tissue.

When the fibroblasts on the surface of a wound are destroyed, the underlying fibroblasts form fibrils which condense to form white connective tissue. At first this connective tissue is red or vascular and will permit a good growth of fibroblasts above, but as it becomes more dense the overlying fibroblasts do not proliferate well because of inadequate blood supply.

Infection

Excessive infection delays contraction and healing because it causes necrosis.

Mild Pressure

Mild pressure applied to a granulating and epithelizing surface promotes healing (92, 94). The optimum pressure is claimed to be that amount which will just compress the superficial capillaries—equivalent, for example, to that which when applied to the finger nail causes blanching. Whether the favorable effect of mild pressure is due to promoting agglutination by mechanically pressing the cells against the fibroblasts or to causing more sticky fluid to be secreted is unknown.

Age

The age of the wound *per se* does not affect healing, but the age of the subject is a factor. In childhood and young adulthood fibroblasts and epithelial cells proliferate more rapidly.

Diet

It is well established (123) that a high protein diet facilitates healing. A *high fat* diet is reported to inhibit. These dietary factors operate chiefly by affecting fibroplasia. An "*acid diet*," which favors a low alkaline reserve, has been reported to favor healing though this was not confirmed by Sandblom (124). It is claimed that the secretion of a wound decreases and is more viscous on an acid diet. An active secretion may dilute and wash away irritants but it is not conducive to the agglutination of epithelial cells or the growth of a cell. Starvation does not apparently delay healing of wounds; repair takes precedence over maintenance. It has been established that *vitamin C* favors healing, probably because it is concerned in the formation of an intercellular cement substance or the condensation of collagen (125). Though the evidence regarding the possible favorable effects of the other vitamins (126) is not so good as that for Vitamin C, the diet should contain an optimum amount of all the vitamins because of their relation to growth and cellular enzyme systems.

Endocrine Glands

Definite hypothyroidism delays healing, as might be expected. The administration of a moderate metabolic stimulating dose of desiccated thyroid increases the rate of healing of acute ulcers of the skin (127). Extracts of the anterior lobe of the pituitary gland have not been found to stimulate wound healing (128); the same is true of testosterone applied locally (129).

Nerves

The preponderance of evidence indicates that sympathectomy promotes healing of skin and gastric wounds (26); the mechanism would be one of more active cellular proliferation in the presence of the hyperemia induced.

Systemic Disease or Disease Elsewhere in the Body

Many reports indicate that healing is delayed by disease elsewhere in the body, but this has not been supported by a sufficient number of controlled experiments.

Nature of the Formative Stimulus

The nature of the stimuli that cause fibroplasia and epithelial proliferation is conjectural. There is no doubt that growth-stimulating and -inhibiting substances exist. A substance which stimulates migration, growth, and reproduction of cells in tissue culture is extractable from cells, particularly embryonic cells; it has been named "archusia" by Burrow

(95). It seems established that if a "second wound" is produced when a "first wound" is proliferating or healing rapidly, the rate of healing of the "second wound" is faster than the "first wound." This suggests that some substance is released to the plasma after the first wound which promotes the healing of the second wound. This hypothetical substance and similar substances present in fluid about wounds have been called "wound hormones" (124, 130). Embryonic extracts have been used to influence the rate of healing of wounds. The results reported are at variance (131, 132, 133, 134).

The exact mechanism by which the remarkably nice balance of growth stimulating and inhibiting factors is maintained is a subject of profound biologic significance and is basic to the problem of repair of a loss of tissue as well as to the problem of tumors.

Abnormal Inflammatory Hyperplasia

During the repair of skin wounds excessive formation of connective tissue occurs in some persons. This tendency to overgrowth of connective tissue, or keloid formation, appears to be inherent in the individual and is particularly common among Negroes. Since Negroes apparently do not develop keloids in healed peptic ulcers, it is doubtful that a tendency to keloid formation is manifested by the connective tissue of the human alimentary tract. However, we have noted keloid formation at the site of intestinal anastomoses in about 4 per cent of dogs.

Chronic Ulcer of the Skin in Man

Most of the chronic nonmalignant ulcers which occur in the skin of man are related to circulatory disturbances. Histologically, five general types of nonmalignant ulcers of the skin are recognized (96) and all these types may be found in chronic varicose ulcers (ulcus cruris) in the leg (97).

a. The hyperkeratotic or calloused ulcer is characterized by hyperkeratosis of the margin. Due apparently to trauma of overtreatment, lack of adequate granulation tissue at the margin, or poor blood supply, the skin becomes cornified to and into the floor of the ulcer. As a result, the cells designed to creep out and cover the granulation tissue cannot do so even when the floor of the ulcer contains healthy granulation tissue. To obtain healing it is necessary to excise the cornified epithelium to produce a fresh wound so that the basal and columnar cells of the Malpighian layer are exposed and can cover the granulation tissue.

b. In the anemic ulcer, the margins are flatter and do not overhang, few mitoses are present, the granulation tissue is feebly developed, and its secretion is scanty. The poor blood supply and scanty secretion lead to desiccation of the granulation tissue and of the new formed epithelial cells

and premature formation of white connective tissue. Poor blood supply of the epithelium at the margin hinders proliferation.

c. THE HYPERTROPHIC ULCER ("proud flesh") is characterized by an overgrowth of granulation tissue and generally is due to the presence of an irritant which stimulates granulation tissue and inhibits the growth of or destroys the epithelial cells.

d. THE HEMORRHAGIC ULCER has a punched-out appearance and is cyanotic or black-brown in color; small hemorrhages are present in the scanty granulation tissue in its floor. The hemorrhagic appearance of the floor is due to rupture of the underlying capillary varices. The epithelium of the margin of the ulcer is partially sclerosed and atrophic, and mitosis is rarely present. Many varicose ulcers start as a hemorrhagic ulcer, after which they are changed, due to treatment or variations in the healing process, to the other types of ulcer described above. These ulcers extend only in width, and their apparent depth is due to edema, small hemorrhages, capillary stasis, and sclerosis, and, later, hypertrophy of the corpus papillare of the margin. Their edges may be somewhat undermined because of infection. Long-standing ulcers due to repeated hemorrhage and necrosis develop a sclerosed base beneath the scanty granulation tissue (96, 97, 98, 99).

e. THE EDEMATOUS ULCER is characterized by a marked edema of the margins of the ulcer and of the granulations which become quite bulbous.

The bacteriologic flora of *ulcus cruris* is variable. The streptococcus and staphylococcus are present along with other bacteria. No relation between the flora and the rate of healing has been found; in fact, Lowenfeld reports that those ulcers which contain the most bacteria heal most rapidly under the same treatment (100, 101). The *ulcus cruris* heals so well after treatment aimed at preventing stasis of blood in the superficial veins that it is difficult to believe that infection is concerned in the chronicity of the ulcer. These observations on chronic ulcer of the skin reveal the importance of an adequate blood supply for the healing of an ulcer. Cells must be nourished adequately if reproduction is to occur. And, it appears that capillary venous stasis is harmful and leads to necrosis almost as effectively as when the arterial supply is completely obstructed to produce gangrene. It is also clear that mild irritation of a wound is beneficial, but excessive stimulation is decidedly harmful.

Two of the types of chronic skin ulcer listed above are not seen in the stomach and intestine. These are the hyperkeratotic and hypertrophic (proud flesh) ulcer. The active chronic peptic ulcer, the type found in the large majority of instances, has a markedly hyperplastic and proliferating epithelium with a floor unsuitable for healing, but cornification does not

occur in the stomach and intestine. A hypertrophic ulcer with granulations extending well above the level of the margin of the ulcer is rarely seen, though the granulations may rarely reach the level of the margin. The indolent ulcer of the stomach resembles the anemic ulcer of the skin. A chronic peptic ulcer which exactly resembles the chronic hemorrhagic ulcer of the skin is rarely seen, although local hemorrhages are observed frequently in the base of the peptic ulcer and bleeding occurs from the margins and into the adjacent mucosa; but an atrophic mucosa is seen only in the indolent peptic ulcer. In the chronic ulcer of the skin the hemorrhages come from ruptured capillary varices which are not present in the hemorrhagic peptic ulcer; in the latter the hemorrhage arises from excessively irritated and digested capillaries, occasionally from the erosion of larger vessels. Edema of the margins of a chronic peptic ulcer is seen with a surrounding gastritis, but marked edema of the granulations is uncommon.

Reproduction of Cellular Elements in the Adult Gastric Gland

Before proceeding to a consideration of the healing of defects in the gastric mucosa, we will summarize what is known regarding the reproduction of the cellular elements in the adult gastric gland. All the epithelial cells of the stomach arise from a mitotic focus located at the bottom of each foveola or crypt. The newly formed cells migrate, on the one hand, toward the surface to become cells of the surface epithelium, and, on the other, toward the bottom of the gland to form mucous chief cells. It is believed that mucous chief cells are transformed into both serous chief cells or pepsin-forming cells and parietal or acid-forming cells. Under normal conditions, mitotic activity is always present in the foci at the bottom of the crypts, an activity that is concerned chiefly in replacing cells lost from the surface epithelium. Whether the pepsin and parietal cells "wear out" and must be replaced is uncertain. Under conditions of injury the serous chief cells may be transformed to mucous chief cells (51, 52, 53).

The observations of Grant (150) on the regeneration of the superficial epithelial cells of the gastric mucosa of the cat have been referred to previously (p. 62). When the surface cells were destroyed in an area by applying 50 per cent alcohol or 1 per cent acetic acid for 5 to 30 minutes, the gaps between the foveolae apparently were bridged by the migration of cells from the bottom or neck region of the foveolae. This migration was evident one or two hours after the infliction of the injury and in 4 to 6 hours the recently migrated cells were forming a new epithelium for the surface and the foveolae.

Mechanism of Healing of Acute Ulcers

Healing of Acute Ulcers of the Stomach

Nature of the Healing

Griffini and Vassale (20) and Poggi (36) investigated the healing of mucosal defects (acute ulcers) in the dog's stomach. Poggi was interested chiefly in the repair of the mucosa after different types of suture. Griffini and Vassale were more interested in the nature of the reparative process. They excised pieces of gastric mucosa in dogs and studied the specimens microscopically for from 1 to 55 days after the operation. They noted that immediately after a piece of mucosa is removed, the size of the defect is decreased by muscular contraction. They found that the glandular cells of the crypts about the margin of the defect undergo mitosis and grow out over the granulation tissue formed in the base, which becomes completely covered with a flattened type of cell. These cells become cuboidal and then columnar, undergo mitosis, and the newly formed epithelium begins to invaginate. This process continues until new gastric glands are formed. It was pointed out that the reparative process was similar to that of embryonic development (55). At the time this work was done the two types of chief cells, the mucous and serous, had not been distinguished; however, they recognized that the "pepsin" cells (serous cells) differentiated from the flattened and cuboidal cells which first covered the granulation tissue.

Bolton, in 1907 (54), studied the healing process of the acute ulcer produced in cats by an injection of gastrotoxic serum. He says: "As soon as the edges of the mucous membrane are separated from the slough, and all the necrotic portions of the glands have been removed by the gastric juice, the cells lining the ducts and bodies of the glands, which are apparent on the raw surface at the edge, commence to proliferate and cover the surface with a single layer of at first flattened and later cuboidal cells (Fig. 25). In this way the edge, which is often inverted, as in man, by retraction of the muscularis mucosae, becomes smooth and rounded. When the edge becomes inverted, the epithelial cells are compelled to grow round the angle between the inverted edge and the base of the ulcer."

Stages of Regeneration

We (22) studied the healing of defects made in the mucosa of a pouch of the pyloric portion of the stomach. This method had the advantage that several ulcers could be produced in the same pouch and direct observa-



FIG. 25. Section through a gastric ulcer six weeks old in the cat produced by gastrotoxic serum. Note the thick layer of connective tissue, the ingrowing layer of flattened cuboidal epithelium, and the small necrotic area in the center. (Courtesy, C. Bolton's "Ulcer of the Stomach," published by Edward Arnold & Co.)

tions made of the rate of healing as affected by controlled mechanical and chemical irritation. Ulcers of uniform size were produced by excision or by the injection of silver nitrate. The healing process after sloughing of necrotic tissue was as follows:

First stage:

1. The mucosal edge of the ulcer is invaginated toward the base by a retraction of the muscularis mucosae and contraction of the underlying musculature; a layer of fibrin is formed and coats the base of the ulcer.
2. The mucosal cells at the edges of the ulcer proliferate.
3. Fibroblasts proliferate at the edges and over the base of the ulcer.

These three processes tend to reduce the diameter and depth of the ulcer, and as a further result

4. The edge of the ulcer is bound down and a bed of granulation tissue is provided for the initiation of the

Second stage:

5. The mucosal cells grow over the connective (granulation) tissue base of the ulcer, forming at first a single layer of mucosal cells, except at the edges where the mucosal cells are several layers thick by the time the base is completely covered.

6. The glands and ducts are then formed, and finally
7. The mucous membrane is practically completely reformed with only a microscopic scar, except when the healing of the ulcer is delayed by mechanical manipulations or acid irritation.

In dogs, in the pyloric mucosa not exposed to acid gastric contents (pyloric pouch), an ulcer originally 1.0 to 1.5 cm. in diameter will heal completely in from 15 to 20 days; the first stage requires from 5 to 7 days. From 3 to 4 weeks are required for sufficient regeneration to occur to render it difficult to see or find the initial site of the ulcer.

When the healing of such ulcers is delayed by manipulating (massaging with fingers, bread crumbs, etc.) the contraction of connective tissue around the base of the ulcer, with further invagination of the mucosa, slowly decreases the diameter of the defect until it is difficult to disturb materially the base of the ulcer by mechanical means.

Dragstedt and Vaughn (9), in studying the growth of epithelium over the surface of the spleen implanted into the stomach, found that the more advanced epithelial cells did not contain mucin or did not stain with fuchsin or mucihematin, though the cells immediately adjacent contained mucin. A relative fibrosis was present in the splenic pulp or base of the exposed area which contained many eosinophilic lymphoid cells.

Morton (29), whose studies confirmed the observations of his predecessors, presents a photomicrograph which illustrates beautifully the cuboidal epithelium covering the granulation tissue, and the early stage of its invagination at the original margin of the ulcer to form glands.

Zones of Regeneration

Ferguson (11), (12), in 1928, using modern techniques, made a careful study of the repair of a defect in the gastric mucosa of the dog and rabbit. He observed the muscular contraction which diminished the size of the original defect. The foveolar cells increased in number at the margin of the defect, were pushed to the exposed surface, and then migrated on to the denuded area composed of fibroblasts. Three zones of regenerated epithelial cells were distinguished. The *first zone* surrounding the initial margin of the ulcer was characterized by deepened and widened foveolae. The *second zone* was more central and consisted of cuboidal cells. The *third zone*, still more central, surrounded the denuded area yet to be covered by epithelium; it was characterized by flattened epithelial cells (Fig. 26). Mucous chief cells, which did not appear until the cuboidal epithelium had invaginated, were the only cell type in the gland tubules in the early stages. The mucous chief cells at the base of these new glands were next transformed into parietal and serous (pepsin) chief cells. Zymogen granules

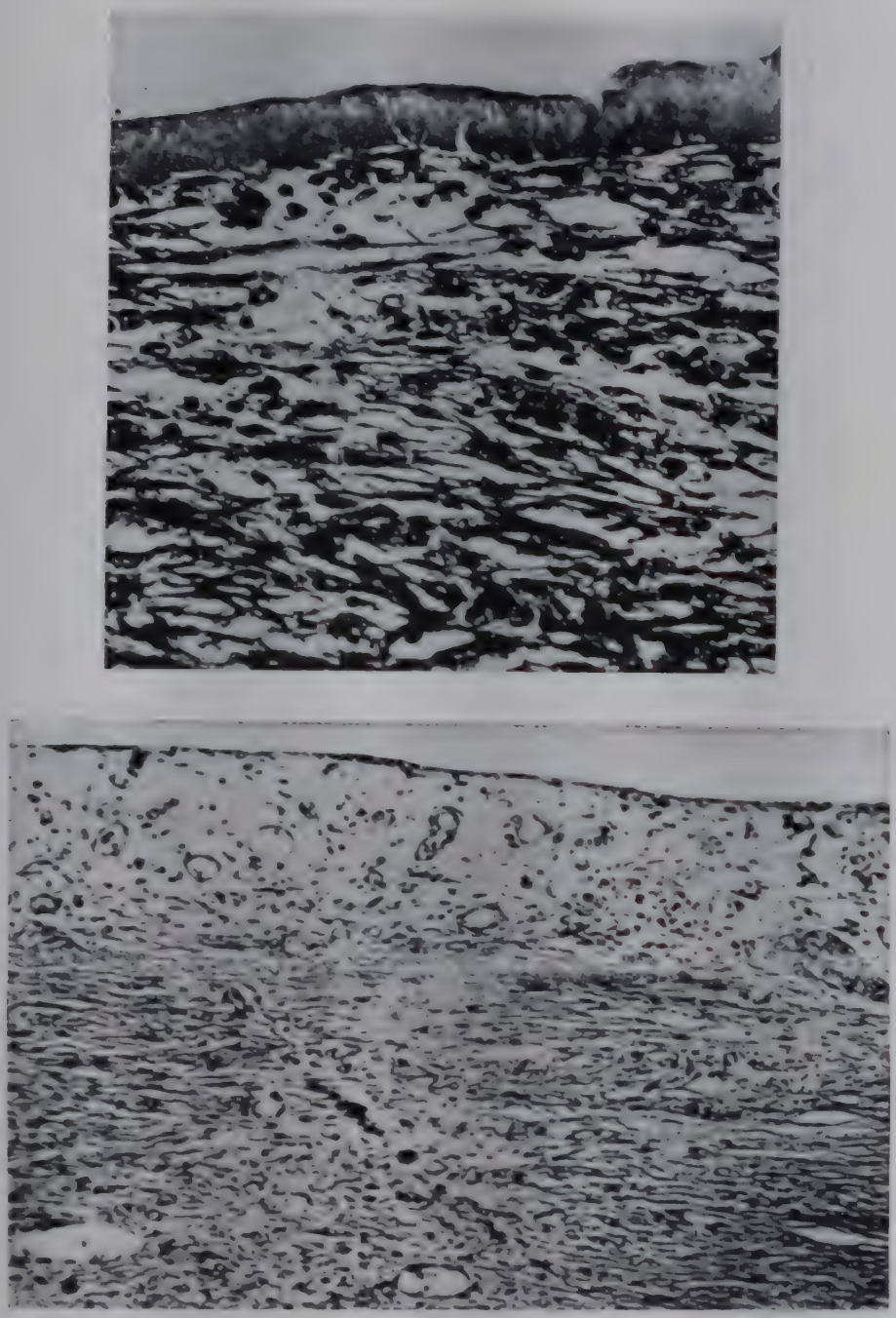


FIG. 26. The section at the top shows the low columnar epithelium of the second zone; the section was made from a seven-weeks old excision ulcer of the stomach in a dog. The section at the bottom shows the flattened epithelium of the migrating cells forming the third zone; the section was made from a two-weeks old lesion of the stomach of the dog. (Courtesy, Ferguson: *Am. J. Anat.*, **42**:403.)

had not appeared in the serous chief cells 12 weeks after the defect was made. It is evident from this study that the new cells arise from foveolar cells; hence, the capacity of the gastric mucosa to regenerate depends on the capacity of foveolar cells to proliferate and migrate.

Using mucicarmine, Ferguson found that "mucin" was present in all the cells; it was confined, however, to the free margin of the flattened cells in the third zone. Ferguson found the three zones of regeneration in all of

his specimens. Griffini and Vassale reported that the denuded area is first covered completely by flattened epithelium. Although the three zones described by Ferguson can be distinguished in most cases, we have observed both types of regeneration. We suspect that when the nutrition is good and there is little source of irritation, as in an ulcer of the pyloric pouch, the flattened cells can cover the denuded area entirely before much differentiation can occur.

Fibrinous Exudate and Fibroblastic Activity

A fibrinous exudate containing leukocytes is formed early. Its presence in sections is variable, depending on the care with which the specimen is prepared and the extent of digestion. Beneath it and in the margins of the ulcer increased fibroblastic activity is evident and granulation tissue appears. If the defect is exposed to gastric contents, areas of necrosis may be found in the granulation tissue; this is not seen in the ulcers produced in a pyloric pouch unless the ulcer is exposed to chemical or mechanical trauma sufficient to cause some bleeding. After the denuded area has been partially covered with epithelium, the fibrinous exudate and occasionally granu'ation tissue extends above the growing edge of the epithelium (11, 56) (Fig. 27). This is not present in all specimens, because, we believe, it has been digested, leaving nothing but fibroblasts or edematous connective tissue beneath.

Muscularis

Everyone has found that the muscularis mucosae and the muscularis do not regenerate. They are replaced with variable amounts of scar tissue, depending on the healing time and the irritation to which the defect was exposed.

Mucous Covering of the Defect

In rabbits in which an excision ulcer has been produced and in which the stomach is opened and not washed, we have sometimes found the defect filled with gastric mucus. This is washed off easily and is inclined to become detached when the specimen is fixed. We have never seen it in the dog, but have never taken special care to preserve it, if present. Dragstedt and Vaughn (9) made special mention of the absence of a mucous coat over the exposed portions of the organs they implanted into the stomach. A mucous layer is absent from all published sections of gastric ulcers we have seen in the literature, nor have we seen it described by surgeons. So, a mucous covering of an ulcer is either relatively uncommon, or it has been washed or wiped away in the handling of the specimens.

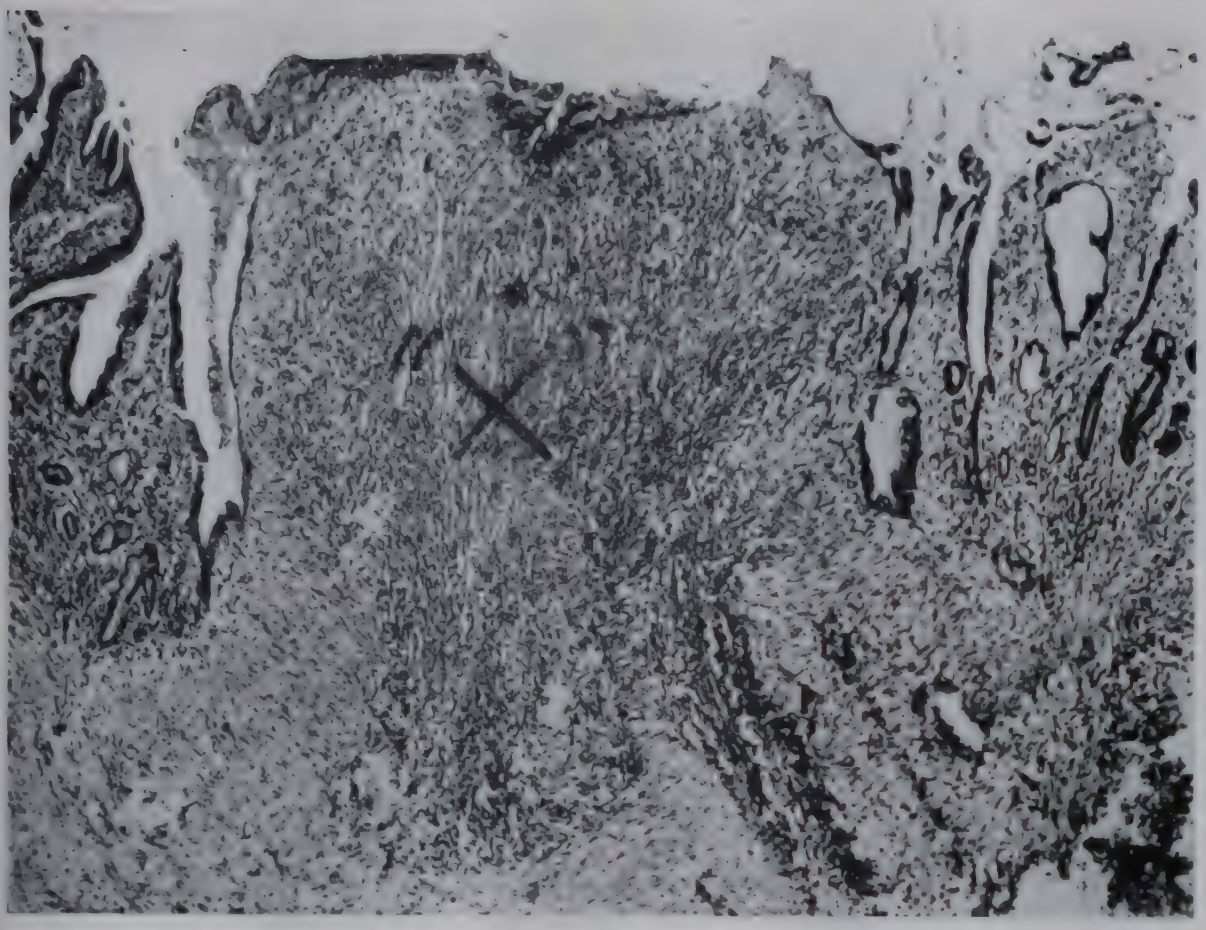


FIG. 27. Section of a healing ulcer after disappearance of the x-ray crater. Note that the crater has been filled with granulation tissue "X" which extends above the original floor of the ulcer. New epithelium is growing in from both sides and attempting to cover the necrotic membrane on the surface of the granulation tissue. Newly formed blood vessels are present in the granulating tissue and the muscularis mucosae is absent. (Courtesy, Crohn, Weiskopf, and Aschner: *Arch. Int. Med.*, **37**:220.)

MECHANISM OF HEALING OF SIMPLE DEFECTS OF THE DUODENAL MUCOSA IN CATS

Florey and Harding (15) produced acute excision ulcers in the duodenum and ileum of cats. The lesions healed by a process that is remarkably similar to that described for the stomach. The repaired mucosa, however, is different from the old in two significant aspects. *First*, the regenerated Brunner's glands are located more superficially in the crypts at the base of the villi rather than submucosally. This probably is due to the failure of the muscularis mucosae to regenerate. *Second*, the villi are reformed but are more bulbous and less closely packed than in the normal duodenal mucosa, and some portions of the epithelium of the villi are identical with that of the surface epithelium of the stomach. Goblet cells are interspersed among the Brunner's gland type of cell. The scarring in this acute type of ulcer is minor (Fig. 28); this is not usually true of chronic duodenal ulcer in the human.

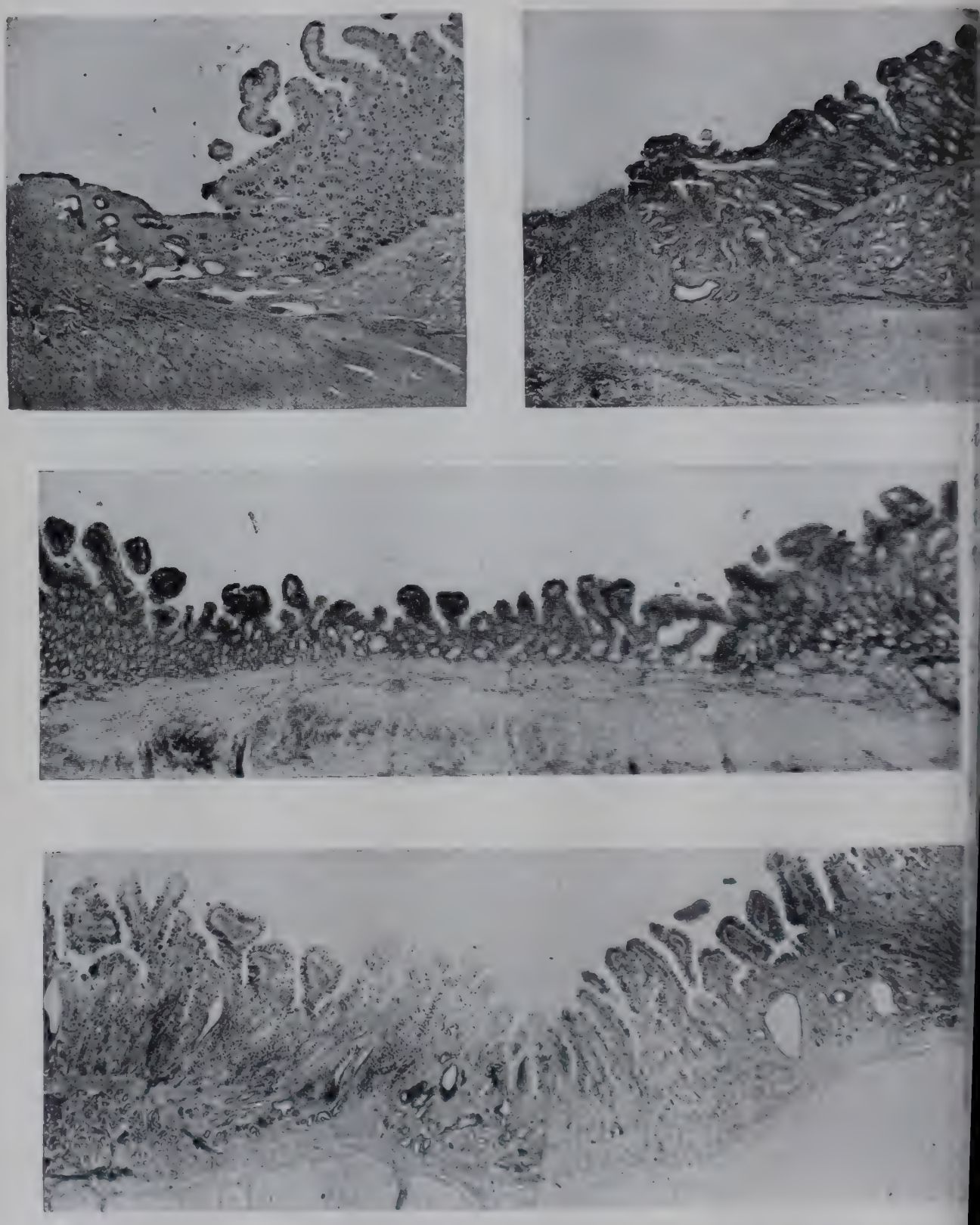


FIG. 28. Showing healing of a duodenal ulcer produced by excision in a cat. (*Top, left*) Edge of an ulcer healing at 10 days. (*Top, right*) Healing ulcer at 21 days; note the break in the muscularis mucosae and the growth of Brunner's glands toward the left of the section. (*Center*) Healed ulcer at 31 days; note regeneration of villi. (*Bottom*) Healed ulcer at 102 days; note lack of muscularis mucosae with the Brunner's glands at the left and the relatively small amount of connective tissue. (× 20) (Courtesy, Florey and Harding: *J. Path. & Bact.*, **40**:214.)

The cells which give rise to the regenerated Brunner's glands and the areas of superficial gastric epithelium on the regenerated villi appear to come from cells of Brunner's glands on the margin of the defect. These cells are regenerated simultaneously with those which form the new villi and arise from the epithelium of the intestinal villi on the margin of the defect. Since the regeneration of the villi and Brunner's glands occurs simultaneously, it is not surprising that patches of cells analogous to the surface epithelium of the stomach appear on the surface of the villi.

Healing of the Gastroenterostomy Stoma in the Dog

Cade (65), in 1901, reported that after a gastroenterostomy is made in the dog a new pylorus is formed in that the fundic mucosa adjacent to the stoma is transformed to pyloric mucosa as regards the character of the glandular elements. Harvey (53) repeated this work making careful histologic studies of the cells. He found that the serous or pepsin cells in the glands extending 7 mm. from the suture line were transformed into mucus-forming cells. One month after the operation the process was reversed, so that 6.5 months after the operation the glands had returned to their initial histologic structure.

Mechanism of Healing of Ulcers of the Jejunum in the Dog

The mechanism of healing of postoperative ulcers of the acute, subacute, or chronic type of the jejunum in the dog has been described by Mann (57), Morton (29), and Mann and Bollman (58). Since their (58) detailed description is so instructive, all of it will be quoted (Fig. 29).

> We found that these ulcers healed quickly and characteristically when protected from contact with the gastric content. When an ulcer had developed in an animal, the site of the lesion was explored, the ulcer observed, and measurements taken; in some instances a specimen for histologic study was also secured. Then the pyloric opening was occluded proximal to the ulcer, thus preventing the passage of the gastric content over it, and the stomach was drained by gastro-enterostomy, the stoma in the jejunum being about thirty centimeters distal from the ulcer.
>
> In our first experiments gross evidence of the healing process was not obtained. This was owing to the fact that it was not realized that the healing tissue was extremely delicate. In these first experiments after protecting the ulcer for a definite period, the animal was killed, the specimen was removed, and the mucosa was washed at the tap in the usual manner. The lesion appeared grossly much the same as at the time it was protected from the gastric content. Histologically, however, evidence of healing could be noted, and furthermore it was observed that most of the healing tissue had been lost. *These observations led us to the use of an extremely careful technic in securing the specimens of healing ulcer.* It was discovered that the healing area must not be touched. The specimen was carefully spread on cork or cardboard and fixed for histological preparation. Gently washing the surface of a healing ulcer with water from a medicine dropper washed away the single layer of mucosal cells covering the granulation tissue, and often the granulation tissue also.

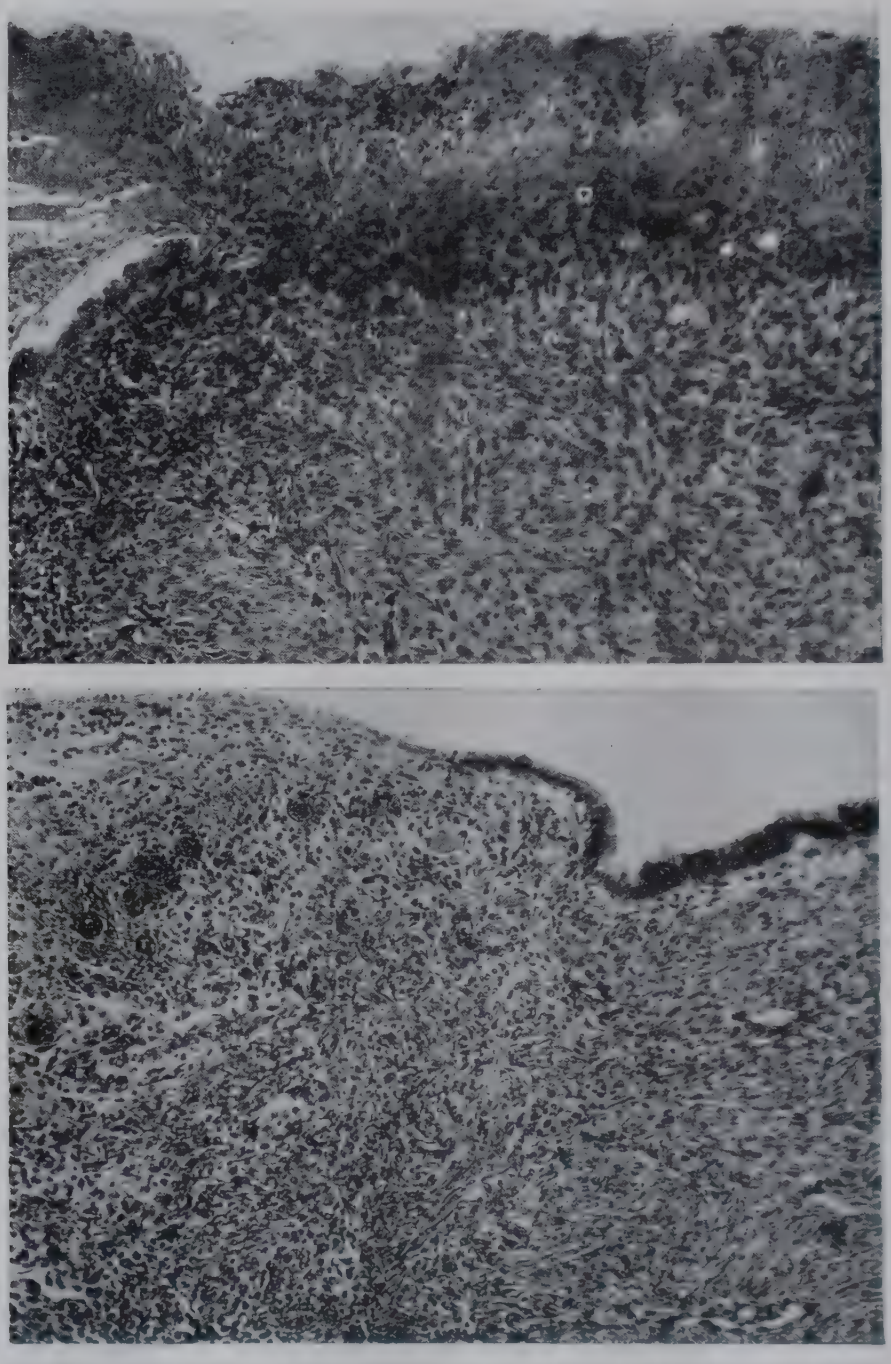


FIG. 29. (*Top*) A section of a postoperative jejunal ulcer before it was protected from gastric contents. Note necrotic debris and granulation tissue. (*Bottom*) Section from the edge of the same ulcer one week later, after protection from the gastric contents. Note the epithelium growing over the granulation tissue. (From Mann, in Eusterman and Balfour's "The Stomach and Duodenum," W. B. Saunders Co.)

We found that the ulcer healed with remarkable rapidity after it was protected from the gastric contents, and passed through a characteristic timed sequence of events. Macroscopically the first changes noted, which occurred within forty-eight to sixty hours after protection from the gastric content, were the disappearance of debris from the base of the ulcer, and the formation of a *protective covering of fibrin* over the whole surface of the lesion. The hard induration (at the base and margin of the lesion) usually had disappeared by this time. The ulcer appeared to become smaller and shallower

owing to the moving in of the edge of normal mucosa and a filling of the base with granulation tissue. These two processes occurred simultaneously. When the diameter of the ulcer had decreased to about half its original size the base of the lesion would be completely filled with a white, glistening tissue which appeared to resemble the freshly exposed surface of a joint. Before the ulcer had completely healed this tissue filled the lesion and projected as a bud above the surface of the mucosa. This projection of the tissue from the base of the ulcer was due to the mucosa growing from the periphery toward the center pushing the granulation tissue filling the base of the ulcer upward. At first the mucosa was thin and smooth but gradually it thickened and became thrown into folds. If the ulcer was small it could not be detected with the naked eye after healing. The whole process of healing would occur in less than thirty days, and the stage of healing would be the same at the same time after protection in the different animals.

The microscopic appearance of the healing ulcer was more characteristic than the macroscopic appearance. The first change observed, which occurred within forty-eight hours, was the disappearing of the cell debris from the base of the ulcers, the decrease in leukocytes in the adjacent tissues, and the formation of the fibrinous layer over the surface. The impression was obtained that the disappearance of the leukocytes was dependent on the protective covering preventing bacteria from penetrating the base of the ulcer. The granulation tissue developed from the base and was very vascular. The connective tissue proliferated, and usually a thin limiting membrane of it formed over the base of the ulcer replacing the first covering of fibrin. The mucosa grew in from the edges over the surface of the granulation tissue. At first the mucosa consisted of a single layer of flat or cuboidal cells on a basement membrane. As the mucosa grew it pushed the granulation tissue out, making a toadstool appearance of the latter. The growing ring of mucosa was thus protected by an overhanging edge of granulation tissue. Often the latter was completely pinched off at the center, although not before it was completely covered with at least a single layer of mucosal cells. As the cells of mucosa increased in number and size, they became typically columnar and the smooth edge was thrown into folds which carried the newly formed blood vessels and connective tissue with it. At first the folds were small and like waves, but as the mucosa grew the typical normal villi appeared. When the ulcer had completely healed three factors distinguished it from normal tissue histologically. The mucosa over the healed area was thinner than normal, the tubules were atypical and rested on a connective tissue base, as the muscularis mucosa does not regenerate.

This description is important to the investigator and the pathologist. It teaches that the defect should not be washed or touched and it should be mounted properly before fixation. In addition, after mounting on a card or block, we have immersed the ulcer face down to fix surface substance first. The descriptions of (a) removal of the slough, (b) the "protective coat" of fibrinous exudate, (c) the simultaneous growing in of mucosa and granulation tissue, (d) the advancing zone of flattened epithelium, (e) the development of glands and villi, and (f) the failure of the regeneration of a muscularis mucosae are similar to that given for the stomach and duodenum. The description emphasizes two points not mentioned before; first, the "protective" bud-like projection of granulation tissue through the uncovered area of the ulcer and its "pinching-off" by the ingrowing

.elium, and, second, the softening of the indurated border of the ulcer
:h may have been due to the decline of inflammation. Apparently the bud-like formation of granulation tissue is not likely to occur in the stomach or duodenum exposed to chemical and mechanical action of gastric contents. According to our observations a distinct bud of granulation tissue occasionally occurs during the healing of an ulcer in a pyloric pouch; Cummins (110) has observed the same process in the human during gastroscopic study of the healing of a gastric ulcer. In the description of the healing of ulcers produced by injecting *Endameba histolytica* into the stomach wall, Joranson and Simons (109) describe the projecting mass of granulation tissue, but they state that it "was reduced only after it became covered with the newly formed epithelium."

As in an ulcer of the skin, the delicately attached proliferating epithelial cells before they invaginate are easily wiped off, and healthy granu-

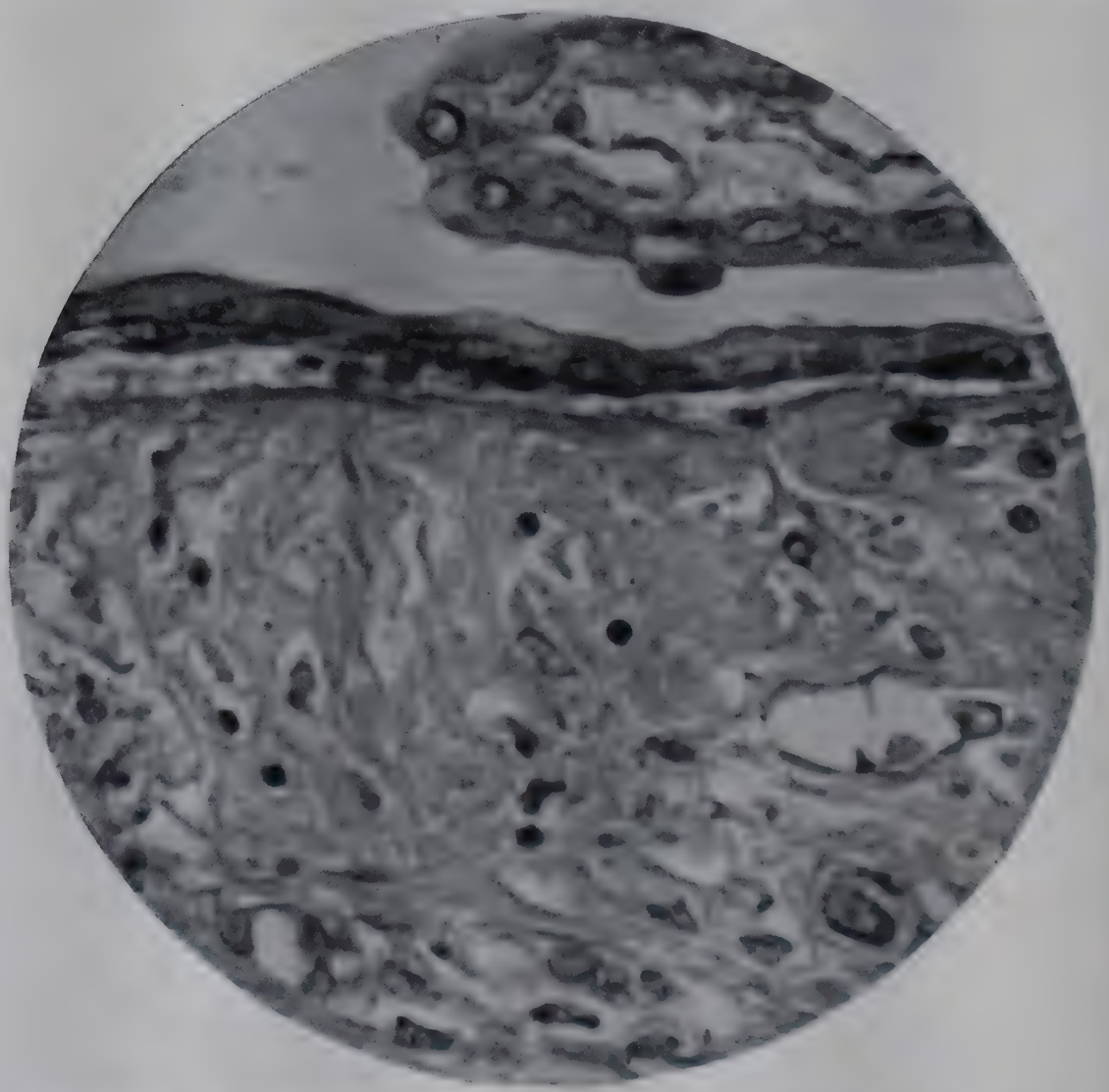


FIG. 30. A stage in the epithelization of a postoperative jejunal ulcer in a Mann-Williamson dog treated with normal urine extract. The flat epithelium is easily separated from the underlying granulation tissue. (Courtesy, D. J. Sandweiss.)

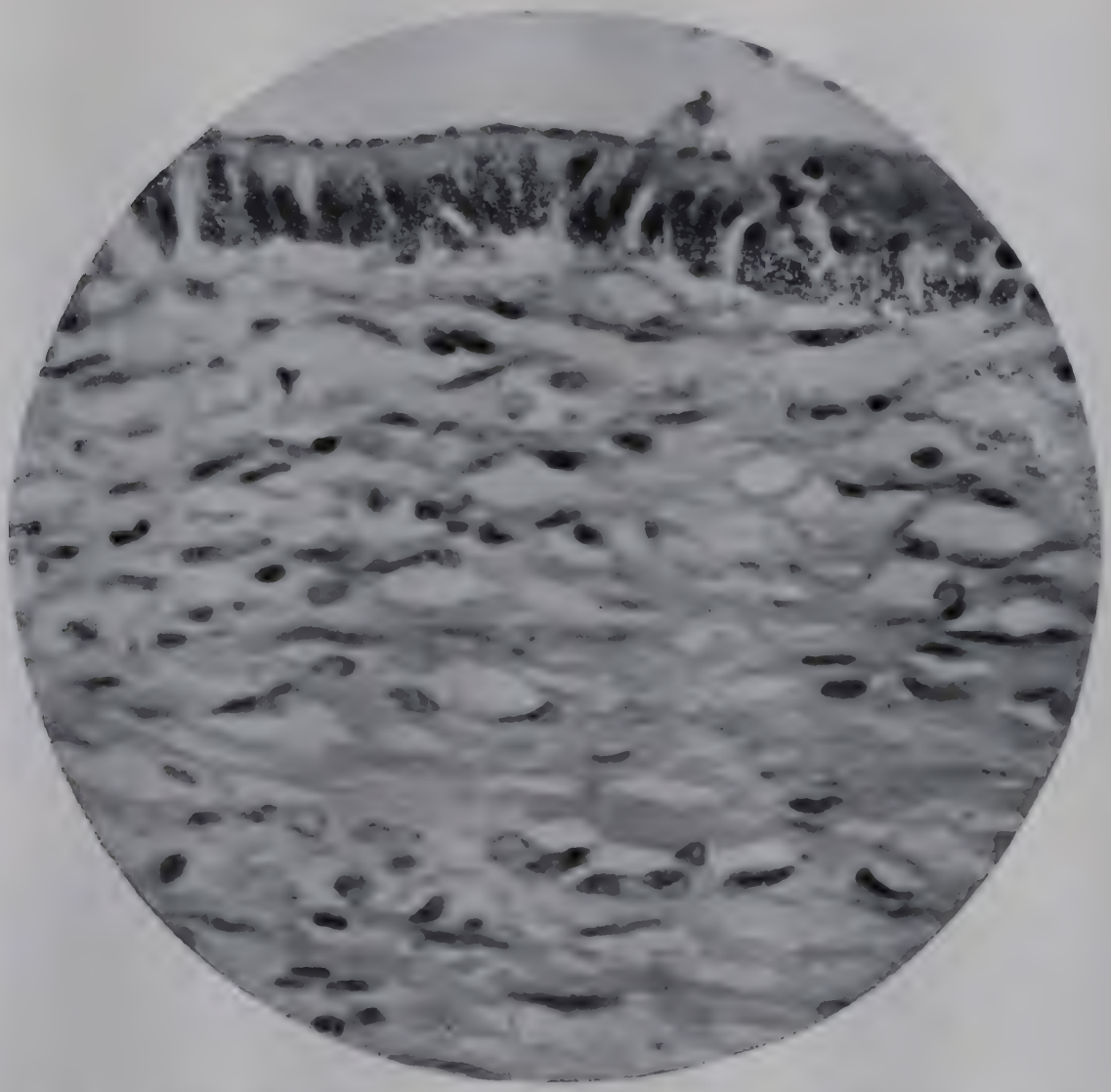


FIG. 31. A later stage in the epithelization of a jejunal ulcer. The epithelium has assumed a columnar form and is now firmly attached to the underlying young connective tissue. Note the similarity of healing in Figs. 28 and 29 and that of an excision ulcer (Fig. 24). (Courtesy, D. J. Sandweiss.)

lation tissue is required for their nourishment. These points are further illustrated in the excellent studies by Beaver et al. (15) of the healing of Mann-Williamson ulcers (Figs. 30 and 31).

Healing of Gastric, Duodenal, and Jejunal Ulcers in Man

ACUTE ULCER

The healing of *acute gastric ulcers* in man has been studied on specimens obtained at autopsy or after the surgical excision of a chronic ulcer in the presence of an acute ulcer. The healing process has been described by a number of investigators (2, 56, 59–63). No essential difference between the healing of an acute ulcer in man and that described above for the dog and

cat has been found (59, 62). In fact, there is no essential difference between the healing of a gastric ulcer and an ulcer of the skin.

The same is true for *acute ulcers of the duodenum* (59, 64), and probably, though no direct evidence is available, for acute ulcers of the jejunum. In a healed ulcer of the duodenum in man the regenerated mucosa resembles that described by Florey and Harding (15) for the cat.

A study of the *healing of a gastroenterostomy stoma* in man within 24 days after the operation has been made in only a few cases (66); it was found that the mucosa in the region of the stoma was almost completely lost, and that the defect at the junction was still present from 14 to 24 days after the operation. Regeneration was evident at the twelfth to fourteenth day. In older cases, the muscularis mucosae was absent, the overlying mucosa resting on connective tissue or the muscular coat. The gastric mucosa adjacent to the stoma may be normal or may show evidence of "gastritis" and contain glands with cystic dilation, the cells of which resemble pyloric glands. Apparently in some cases, irritation or some other factor can prevent the retransformation of mucus-forming cells to pepsin-forming cells as described by Harvey in the dog. This may ex-

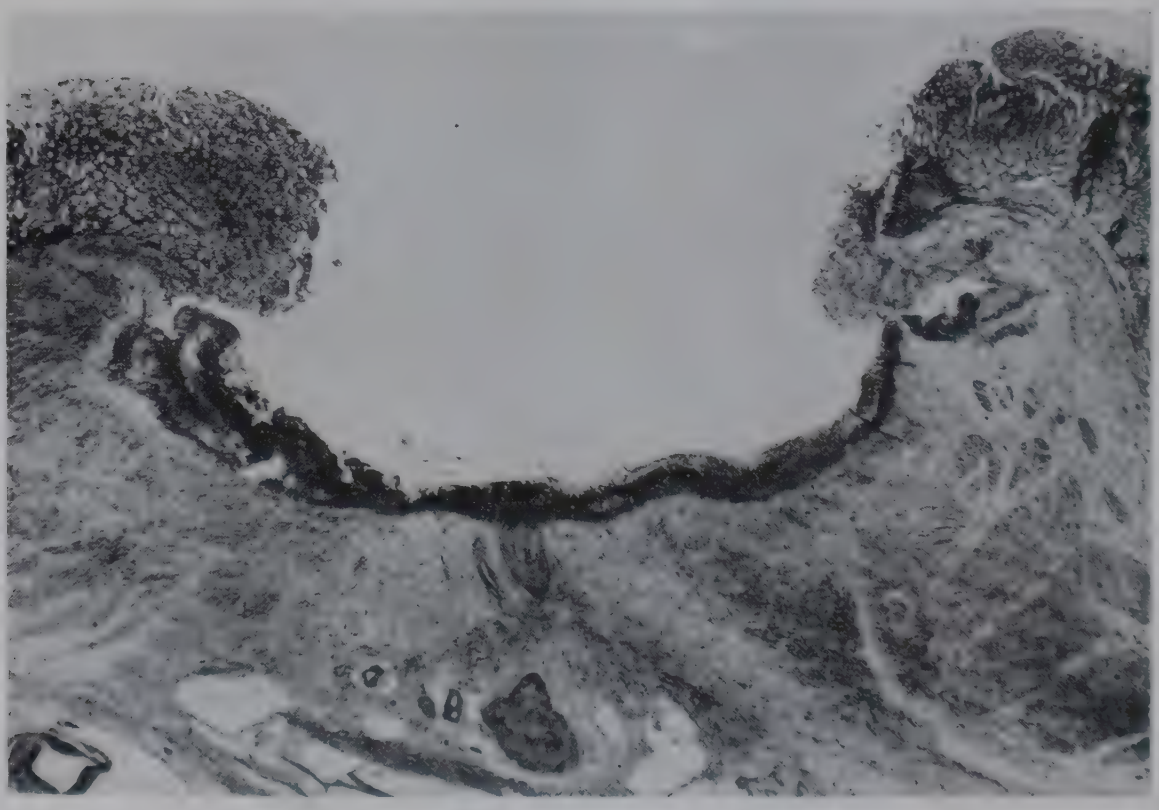


FIG. 32. A chronic gastric ulcer with undermined margins. Note the zone of darkly stained fibrinoid necrosis in the floor, beneath which is granulation tissue, and in the center of the floor beneath the fibrinoid zone the artery closed by endarteritis. On the right, muscular coat forms a part of the margin and floor of the ulcer. (Courtesy, Hurst and Stewart: "Gastric and Duodenal Ulcer," Oxford University Press.)

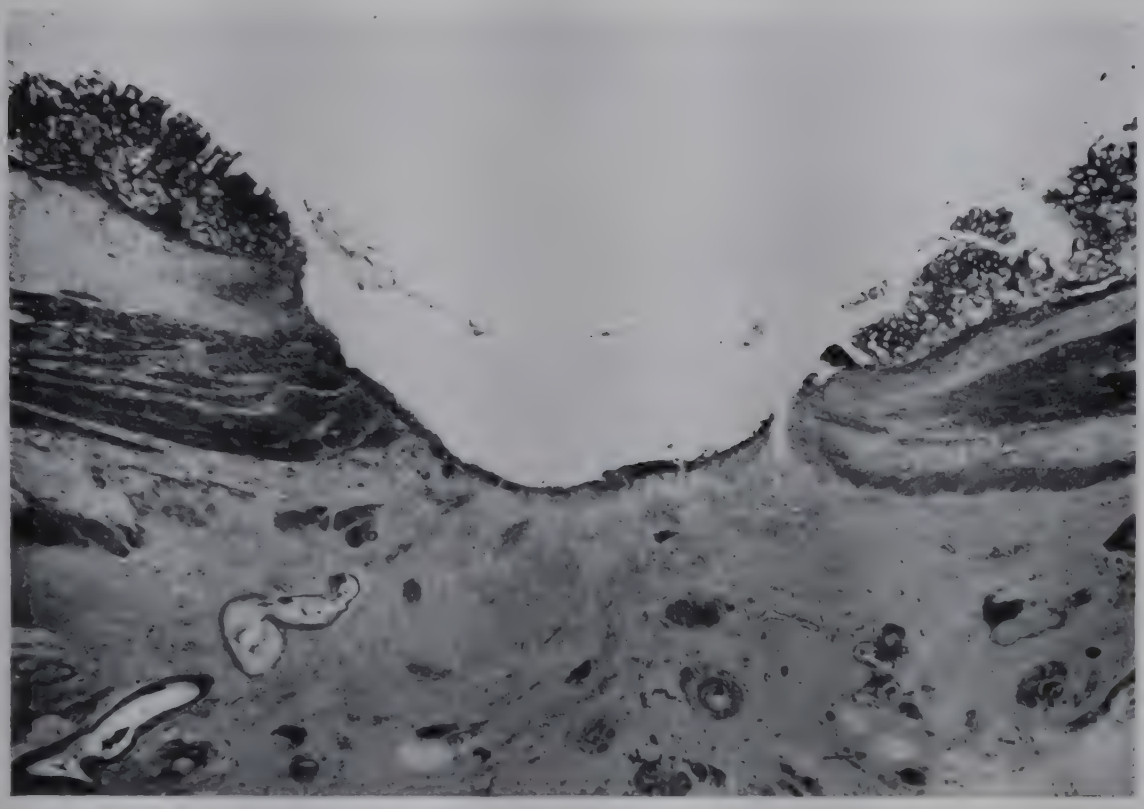


FIG. 33. Early stage of healing of a chronic gastric ulcer in man. The crater has flattened and epithelization has started on the right where the muscularis mucosae and muscularis almost approximate. (Courtesy, Hurst and Stewart: "Gastric and Duodenal Ulcer," Oxford University Press.)

plain the discrepancy between the observations of Cade and Harvey. Pyloric glands have also been described on the jejunal side of the stoma, but these may be Brunner's glands which extend into the upper jejunum in man (66). A cystic glandular structure may also develop in some cases on the jejunal side in conjunction with jejunitis.

CHRONIC ULCER

The healing of chronic gastric and duodenal ulcer in specimens obtained at autopsy and on surgical resection has been studied by a number of investigators (56, 59, 60, 61, 63, 68–72, 74–78, 83). It is generally agreed that the healing process is the same in acute and chronic ulcers of the stomach and duodenum. The chief difference is that a chronic ulcer frequently heals more slowly and with very obvious scarring. However, the regenerated mucosa is more likely to contain patches of an intestinal-like epithelium, and the new-formed glands are more likely to penetrate or be misplaced into the muscularis mucosae or the fibromuscular tissue. These misplaced and heterotropic glands may undergo cyst-like changes, as occur in some instances on the gastric and intestinal side of a gastroenteric stoma. If the underlying scar is large and dense, the regenerated mucosa is thinner than normal and the gland tubules are irregularly

placed; and in the stomach the gland cells tend to remain undifferentiated or mucoid in type (Figs. 32–35).

It is worthy of emphasis that the chronic ulcer, with the exception of the "indolent" ulcer, almost uniformly shows evidence of an attempt to heal at some point in its margin. According to Stewart (59), the "indolent ulcer" shows little evidence of inflammatory reaction in its floor or margin, fibroblastic proliferation is not marked, the scar tissue is dense, and the epithelium at the margins manifests relatively little activity. This type of ulcer causes few or no symptoms, and, because its margins flatten, it may be misinterpreted as a healing ulcer.

Histopathology of a Chronic Peptic Ulcer

It is not our intention to discuss the pathology of chronic peptic ulcer extensively. This has been done by Stewart (59), Hauser (63), and Askanazy (78). However, attention may be directed to certain points in the histopathology of chronic ulcer which are of interest in relation to its slow rate of healing. These points will be mentioned, keeping in mind that they may represent only the effects of repeated chemical and mechanical insult rather than a primary cause of delayed healing.

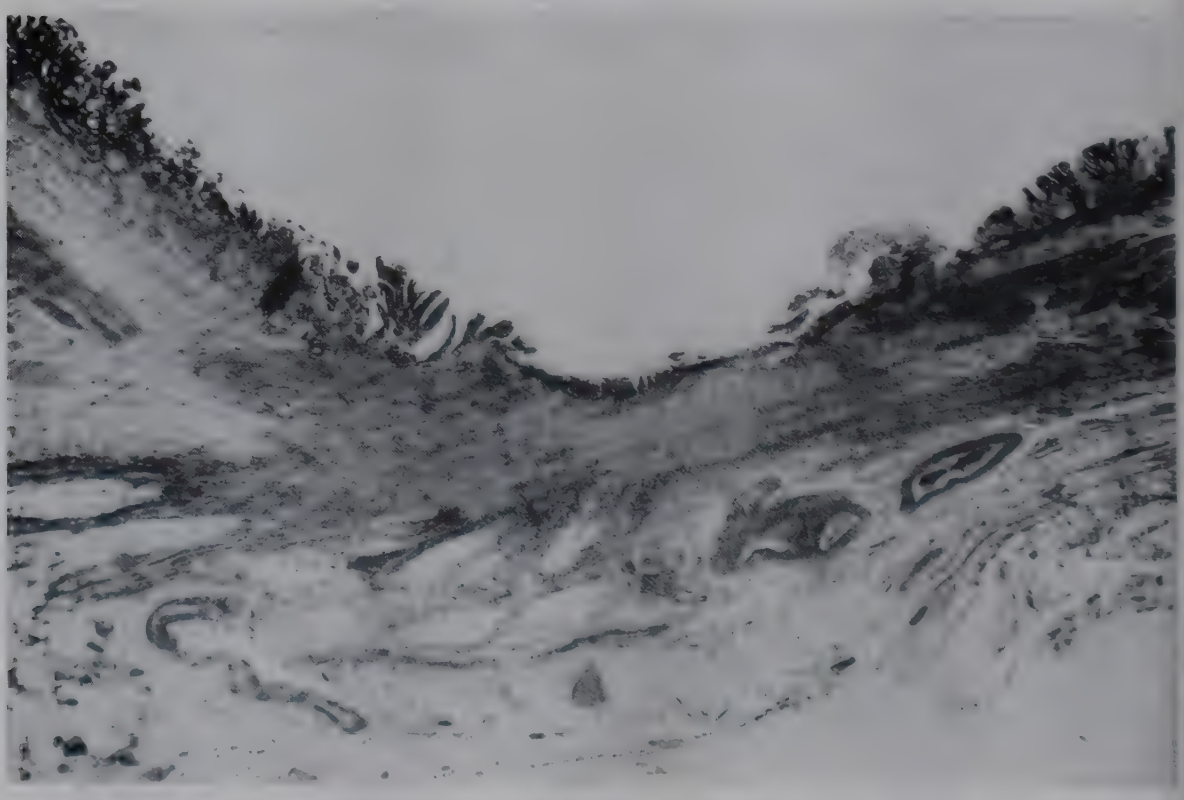


Fig. 34. Showing a later stage of healing of a chronic gastric ulcer in man. The margins but not the center of the ulcer have epithelized. The well-developed villous appearance of the marginal epithelium so close to the unepithelized center of the ulcer indicates that the ulcer had been healing very slowly. (Courtesy Hurst and Stewart: "Gastric and Duodenal Ulcer," Oxford University Press.)



FIG. 35. Showing a well-healed ulcer with a very dense fibrous tissue in a gap of the muscular coat. The new mucosa is not quite so thick as the normal, which is frequently the case. (Courtesy, Hurst and Stewart: "Gastric and Duodenal Ulcer," Oxford University Press.)

Margin

Except in the "indolent ulcer," the epithelial cells in the foveolae of the margin of a chronic ulcer show marked proliferation, so marked at times that it resembles malignant tissue. Apparently these cells are receiving an adequate blood supply. Retraction of the underlying muscularis mucosae, either because of contraction or digestion, is at times so marked that the mucosa becomes inverted and lies on the floor of the ulcer. Frequently lymphoid cells are found in large numbers on each side of the muscularis mucosae. The submucosa is thickened by edema and fibrosis, which elevates the margin of the ulcer. Leukocytes are present; eosinophils are particularly characteristic. The capillaries may be filled with polymorphonuclear leukocytes. Bacteria may be found in the inflamed margins (64, 79–82, 84, 85).

Floor or Base

The floor of the chronic ulcer usually is divided into four layers after Askanazy (78). The *first zone* consists of fibrinous or purulent exudate containing leukocytes, bacteria, and sometimes fungi, much like that found in the acute ulcer. It is easily washed away. The *second zone* consists of fibrinoid necrosis. It is structureless and contains debris of leukocytes.

fibroblasts, variable numbers of bacteria, and perhaps fibrin and blood pro tein. Sometimes the debris of nerves and blood vessels is present. This zo may also cover the submucosa at the margin or extend to the mucosa. Th *third zone* consists of granulation tissue to which the fibrinoid necro substance is closely adherent, resembling a scab. The fibrinoid zone aris at the expense of the granulation tissue. When the fibrinoid zone is thi the granulation tissue is relatively thin and avascular; when absent, t granulation tissue is vascular and typical of a granulating wound. Eosi phils are present especially at the margins in relation to the coagulat protein of muscle fibers; their presence is typical of aseptic type of necro and of chronic or subacute ulcer in contrast to acute ulcers. Lymphocy and plasma cells are also present, but polymorphonuclear leukocytes chiefly confined to the fibrinoid zone. Bacteria have been found to present by several investigators (64, 79–82, 84–86). The *fourth zone* is scar tissue layer.

Blood Vessels (59, 63, 76)

In acute ulcers the small blood vessels bleed, but are soon plug with thrombi or fibrin. The vessels, if healing is retarded, show react changes. The *small arteries* exhibit a proliferative change or an obliterat endarteritis. The lumen may be markedly reduced or completely literated (Fig. 33). If obliterated, the newly organized tissue frequ becomes canalized with blood vessels. Sometimes there is a nonpathol decrease in size of the lumen of the blood vessel with folds in the in due to decreased blood flow caused by a contraction of the under musculature. These changes in the arteries are found most frequen those vessels which supply the ulcer floor. The veins are more like show thrombosis and organization of the thrombus which later may come canalized. Thrombosis, except in the small vessels in the fib zone, is less frequent than endarteritis. Obliterative endarteritis is common to duodenal ulcer on the posterior than on the anterior wall

These changes reduce the tendency to hemorrhage. However, he rhage may occur in an ulcer healing at the margins and penetrat the center. A saccular aneurysm usually precedes the rupture of an Th occurrence of endarteritis and thrombosis in the veins explains fewer deaths occur from hemorrhage than from perforation. Howe thickening of the arterial wall would interfere with its contractio predispose to more prolonged hemorrhage. So, though these in nents of the blood vessels are definitely protective in nature, they predispose to prolonged hemorrhage or delay healing by reduci blood supply.

Nerves

The submucosal plexus (Meissner's) is always involved in ulcers; and en the main musculature is entered the subserosal and the muscular xus (Auerbach's) is also involved. A number of investigators (32, 59, 76, 78, 87, 88, 90, 158) have described changes which occur in the ves. The changes are manifested as (a) perineural inflammation and rosis which is quite constantly found, and (b) cicatrix neuromata of periarterial, Auerbach, and other nerve fibers. Intraneural inflam- tory changes are infrequent. Ganglionic cells may show degenerative anges (155). Nerve fibers appear to be quite resistant to digestion and rphologically normal fibers are sometimes seen up to the fibrinoid ne.

Scars

Erosions heal without scars. Acute ulcers which heal rapidly leave no ssly detectable scar unless the ulcer was over 1.5 or 2.0 cm. in diameter. en then, frequently the scar can be found only by microscopic exami- tion or by using the transillumination technique of Bolton (56). The nount of scar tissue is generally directly proportional to the size and gree of delayed healing of the ulcer.

The extent of the permanent *deformity* depends on the amount of scar sue and especially the location. A large saddle-ulcer of the lesser curva- re produces considerable deformity. A chronic duodenal ulcer prac- ally always causes some permanent deformity which alters the motility ttern from that of a normal duodenal antrum. If the deformity is arked, duodenal stenosis may result; this is most likely to occur when cers of both the anterior and posterior walls heal. When the ulcer is thin 0.5 inch of the pylorus, the contraction of the scar tissue may de- rm the pyloric ring, causing some stenosis. Sometimes the scar may pull e pyloric ring toward the duodenum producing a pouch on one or both les of the scar (pseudodiverticulum). Such pouches are usually in line th the lesser or greater curvatures (59) (Fig. 36).

Extension of Ulcers

Both acute and chronic ulcers may sometimes extend laterally, or come deeper, or both, quite rapidly. This is known to occur in man well as in experimental ulcers in animals. At autopsy in even good aling may be seen all around the margins of an ulcer which centrally s eroded an artery or has penetrated the serosa, causing death from morrhage or perforation (59).



FIG. 36. Showing a healed posterior wall ulcer with a scar which has pulled the pyloric ring toward the duodenum, producing a pouch of the duodenum on each side. (Courtesy, Hurst and Stewart: "Gastric and Duodenal Ulcer," Oxford University Press.)

Figures 37 and 38 show a case of rapid lateral extension and penetration of a jejunal ulcer in a dog. In figure 36 the ulcer measured 5 by 6 mm. and had penetrated only to the circular musculature, exposing the muscle bundles. Forty-eight hours later, immediately after death, the defect in the mucosa measured 14 by 26 mm. and in the serosa 6 by 8 mm. In the interval the animal had received only water by mouth. The ulcer was on the posterior wall and had been exposed by an incision on the anterior wall.

Rate of Healing of Acute and Chronic Ulcers

RATE OF HEALING OF ACUTE AND CHRONIC ULCERS IN ANIMALS

The rate of healing of defects in the gastrointestinal mucosa, especially of the stomach, has been studied extensively in the dog. However, the studies do not approach the accuracy and precision of those on the skin.



FIG. 37. Photograph of a subacute jejunal ulcer made at an exploratory operation. The ulcer measured 5 by 6 mm. and extended to the circular musculature.

The earlier students of the problem (7, 20, 27, 34, 37, 108) made relatively small (1.0 to 1.5 cm. in diameter) defects in the gastric mucosa and observed that they healed in from 5 to 30 days. Hemmeter (21), in the course of experiments demonstrating the possibility of visualizing small defects in the gastric mucosa by x-ray, noted that such defects were completely healed in two weeks. Ulcers of variable sizes were used by these investigators; and, as indicated above, the size of a defect influences the rate and mechanism of healing; in addition only a few animals were used.

Erosions and Defects in the Surface Epithelium

Grant (150) found that when the surface epithelium alone is destroyed the exposed stroma may be covered with a layer of epithelial cells in one or two hours and the formation of a new epithelium was well advanced in four to six hours. Gaps in the surface epithelium are covered at rates for from 0.2 to 0.4 mm. per hour. Erosions extending to the muscularis mucosae usually heal in two or three days.

Small Acute Ulcers

POSITION. Studies on the rate of healing of small acute ulcers have not been as systematic as the subject warrants. Dragstedt (8) made acute ulcers from 1.0 to 1.5 cm. in diameter in the mucosa of a Pavlov pouch; healing occurred in 5 to 15 days. Ulcers of a similar size were made in the duodenum in its natural position; healing occurred in 20 days. We (22) produced ulcers 1.0 to 1.5 cm. in diameter in the fundic, pyloric, and

duodenal mucosa with the organs in their natural position using five dogs for each site; in addition we studied healing of acute ulcers of the same size produced in the mucosa of a pyloric pouch in 10 dogs. The ulcers in the fundic mucosa healed in 9 to 13 days, in the pyloric mucosa in 12 to 18 days, in the duodenum in 16 to 24 days, and in the mucosa of the pyloric pouch in 15 to 21 days. Matthews and Dragstedt (153) found that ulcers made in the pyloric mucosa of dogs with silver nitrate healed in 15 to 18 days. Yano (47), using the rabbit, found that ulcers made with a hot iron healed more rapidly when made in the fundus than along the lesser curvature. Walker (44) reported that defects in the pyloric region heal more rapidly than defects in the fundus in rabbits. Morton (29) observed in the dog that defects made in the fundic, pyloric, and duodenal mucosa 2 cm. in diameter healed in two weeks. Under adverse conditions, ulcers made on the lesser curvature healed more slowly than those on the greater curvature. McIlroy (138) observed in the cat that defects made in the pyloric mucosa heal more slowly than ulcers made elsewhere in the stomach. Hughson (143) reported that ulcers made in the pyloric portion of the lesser curvature heal more slowly than ulcers made elsewhere in the pyloric mucosa. Bolton (56) found no difference in the rate of healing of



FIG. 38. Photograph of the same ulcer shown in figure 37 made 48 hours after the exploratory operation. The mucosal defect measured 14 × 26 mm. and the perforation 6 × 8 mm.

ulcers produced in different portions of the stomach; the ulcers healed within three weeks regardless of their location.

These data demonstrate clearly that acute ulcers or defects in the gastric and duodenal mucosa heal at a rate of from 1 to 2 mm. per day. The healing is slightly more rapid in the duodenum than in the jejunum, somewhat more rapid in the pylorus than in the duodenum, and slightly more so in the fundus than in the pylorus. It would appear that there exists a gradient of healing potential inversely proportional to the gradient of susceptibility to acid injury. Thus the respective healing times for lesions 1.0 to 1.5 cm. in diameter are approximately: jejunum, 25 days; duodenum, 20 days; pylorus, 15 days; fundus, 10 days.

Large Acute Ulcers

The rate of healing of large defects in the gastric mucosa has not been studied extensively, and the observations reported vary considerably. Matthes (27), in two experiments, produced a defect 6 cm. in diameter and found that it was reduced to 2.5 cm. in two weeks and was healed in four weeks. Tixier (43) and Carnot (3) found that a defect 10 cm. in diameter will heal completely, and the latter author reported that a defect 5 cm. in diameter healed in 20 days when the animal was treated with embryonic extract. Santy (40) reported complete healing of a defect 7 cm. in diameter in one month. According to Michon and Magron (28), a defect 8 by 10 cm. was reduced to a small ulcer within one month and a defect 8 by 8 cm. was completely repaired in seven months. Ferguson (11) made several defects approximately 6 cm. in diameter; one had healed in six weeks and others at 10 to 12 weeks. He estimated that defects 6 cm. in diameter heal at a rate of 2.25 mm. per week.

It would appear from the reports available that the rate of healing of defects 5 cm. or more in diameter is much more variable than defects 2 cm. in diameter. The best data are supplied by Ferguson. The range for a 6 cm. defect is from one month in Matthes and Santy's cases to 2.5 months in Ferguson's cases.

Such variation might be expected because (a) a large defect may be exposed to more trauma, (b) there is a limit to the amount which the size of the initial lesion can be decreased by contraction of the musculature, and (c) there must be some limit to the extent of contraction of the connective tissue formed in the base of an ulcer.

Attempts have been made to evaluate the contribution to healing made by the initial decrease in the size of the defect by *contraction of the musculature*. Matthes (27) stitched a porcelain ring to the serosa of the stomach and excised the overlying mucosa. Healing occurred in one month, or the usual time, in the two experiments performed. Litthauer (135) attempted to ac-

complish the same end by removing the muscularis down to the serosa. H lesions, as well as similar ones produced by Bolton (108), healed in the no mal time of one month. Kirch and Stahnke (25), who used Litthauer technique, reported that inclusion of the muscularis in the defect delaye healing, which was complete, however, within five months. We (91) place silk sutures in the normal mucosa around the edge of excision ulcers in t pyloric antrum of rabbits. Measurements made at the time of operati and again at the time of necropsy 10 days later revealed that of the 68 p cent reduction in the size of the ulcer, 54 per cent was due to contracti and only 14 per cent to epithelization.

In the case of skin wounds there is a limit to which the connective tis may contract and reduce the size of the defect. When this contraction h reached its limit, epithelization is slow when the edges are 1.5 cm. ap and epithelization ceases when the edges are 2.0 to 2.5 cm. apart. *If th applicable to the gastric mucosa, one should not expect a completely contracted loused ulcer 2.5 cm. in diameter to heal.* At least, by analogy with the skin, i possible to understand why the presence of an excessive amount of wi connective tissue in the floor and margins of an ulcer can be associated w delayed healing; in addition it probably decreases the local blood sup

Chronic Ulcers

The rate of healing of a subacute or chronic ulcer, except those scribed in the rabbit (p. 157), has been studied only in the case of the p operative jejunal ulcer in the Mann-Williamson dog (p. 135). In this c when the ulcer is removed from exposure to gastric contents, healing curs within 30 days (29, 58).

Rate of Healing of Acute and Chronic Ulcers in Man

Erosion and Acute Ulcers

Wolf and Wolff (102), studying a patient with a gastrostomy, obse an erosion 4 mm. in diameter and 1 mm. deep heal in three days. By troscopic observation a "shallow ulcer" has been observed to heal w 15 days (112).

Chronic Ulcer

Chronic gastric ulcers tend to be larger than acute and subacute ul though occasionally the latter types may measure 2.5 cm. in diameter Even chronic gastric ulcers do not tend to be large. The diameter of 7 cent of 638 surgically excised chronic gastric ulcers was 2.5 cm. or les remainder ranged from 2.5 to 4.9 cm. in diameter (114). At aut

tric ulcers as large as 10.0 to 12.5 cm. (long diameter) have been found
).

Duodenal ulcers tend to be smaller than gastric ulcers. Twenty-five
opsy specimens of ulcers on the posterior wall measured by Hurst and
wart (59), had an average size of 1.6 by 1.2 cm., and on the anterior
ll 1.1 by 0.8 cm. Ulcers on the posterior wall, however, may be as large
2.5 cm. in diameter.

There is a surprising paucity of controlled observations on the rate of
ling of chronic gastric and duodenal ulcer. Most of the reports on the
ject of disappearance of a niche revealed by roentgenologic examina-
n are pointed toward proving that either the presence of a niche is not an
lication for surgical intervention, as was once argued, or a particular
dical management is effective. In many reports the size of the niche and
approximate time of its disappearance are not provided, and roent-
nograms were not made at regular intervals.

The paucity of data on this subject may in part be due to doubt re-
rding whether the disappearance of the niche indicates healing. The dis-
pearance of the niche, along with the absence of occult blood in the
ols, is the most readily obtained evidence of healing. In the absence of
ect inspection and histologic examination, it is the best evidence one can
tain.

We have been able to find only two reported instances in which a gas-
c ulcer was examined histologically soon after the disappearance of the
he. In both of the cases the ulcer was almost but not completely epi-
lialized (118). However, the disappearance of a niche in the stomach
s been correlated with gastroscopic examination in 18 cases. In 12, or 67
r cent, the ulcer was reported as being epithelialized soon after the dis-
pearance of the niche; in 5, a shallow ulcer was still present (116, 117).

Healing times were noted by several authors in evaluating special
ethods of treatment. Among these are Buckstein (156) who described a
se of gastric crater treated by frequent duodenal tube feedings which was
bsequently visualized at the end of six weeks of treatment and question-
ly seen also at 8 and 15 weeks. Einhorn (152) also reported disappearance
the niche in five cases of gastric ulcer in 2, 2, 4, 7, and 10 weeks after
anagement by duodenal feeding. Fifteen cases of gastric ulcer were fol-
ved gastroscopically by Freeman (160) in evaluating duodenal feeding
erapy: he reported the average time of disappearance of the crater
stroscopically as four weeks, but added that some cases required a "little
nger time"; a control case on a "gastric diet" instead of duodenal feed-
gs still showed the lesion present after six weeks. Co Tui et al. (151), in
aluating their use of protein hydrolysate treatment reported the radio-

logic disappearance of four duodenal craters in from 10 to 25 days after treatment and the average disappearance time of eight gastric lesions as 19 days with a range of 10 days to one month; three other gastric craters were smaller in 10 to 15 days.

Several writers reported data on healing time but their repeat x-ray studies were done at intervals too long for accurate estimation. Hamburger (67) reported a case each of gastric and duodenal ulcer which were checked by x-ray after three months' treatment and found to have disappeared. Diamond (147) also presented evidence of crater disappearance after treatment with a modified Lenhartz diet in 10 gastric ulcers in from two months to two years; another of his cases revealed x-ray disappearance of the crater in three weeks and another in seven weeks. Nicholas and Moncrieff (115), using an average time of six months between their first and second x-ray examinations, presented 11 cases of "healed" gastric craters after six months of undescribed treatment; four more craters had decreased in size but were found healed 3½ months later and two had remained stationary, one of which was subsequently found to be healed after another 3½ months' treatment; four recurrences of the 11 "healed" craters were noted 9½ months after their original films; no correlation could be found between duration of symptoms and time of healing. White (157) concluded that age had no effect on healing (age range was 40 to 60 years) and that the size of the crater and duration of symptoms also had no effect; he reported disappearance of three medium-sized gastric craters in from two to six months, two large gastric craters in one to six months, and one small stomach ulcer in one week; he used a modified Sippy diet.

Healing time was mentioned incidentally by several authors. Brown (145) mentioned the disappearance of two craters in the stomach in 12 weeks and in 37 days after a strict Sippy regimen. The disappearance of one gastric and two duodenal craters was noted by Golden (140) in 44 days, 3 weeks, and 6 months, respectively, after bed rest and Sippy diet. No radiologic evidence of crater was found by Hurst and Briggs (113) in three gastric cases after treatment of undisclosed nature for one month, two months, and three years. Tanner (2) made the general statement that gastric ulcers will heal gastroscopically in three to six weeks in some cases of acute, subacute, and moderate-sized chronic lesions but added that many lesions heal slower; he reported a case of gastric crater that became less than one-fourth its original size in three weeks and another that remained unhealed in 12 weeks; no details as to type of treatment were included. Employing a modified Sippy therapy, Dale and Redichen (111) found that four to nine weeks of treatment were required for disappearance of the niche in five gastric cases and six weeks in two duodenal cases.

The largest numbers of cases were reported by Ohnell (119) and by

Templeton (116). The former recorded disappearance of the niche in 33 cases of gastric ulcers in an average of 40 days (range 14 to 100 days) after rigorous treatment consisting of six weeks of bed rest and a diet of milk, cream, eggs, and fish with Vichy water; he stated that large craters tended to heal slowly but there was poor correlation between size of crater and rate of healing; no attempt was made in this study to take repeat films at specific time intervals. Templeton reported the disappearance of the crater in 36 duodenal ulcers in from 1 to 20 weeks; again, he could make no correlation between size of crater and time of healing; there is no mention made by this author of the frequency of x-ray examinations nor the amount or type of treatment given.

We (110) reported the time of disappearance of 69 duodenal and gastric craters in a military hospital under well-standardized conditions of treatment. As only six of these cases were gastric ulcers, the average healing time of 42 days in this group was not considered a reliable average. For the 63 duodenal craters, the average time for x-ray disappearance of the niche was 40 days; excluding the case of a 66-year-old civilian dependent whose crater persisted up to 230 days, the average was 37 days, with a range of 13 to 68 days. However, inasmuch as the first routine follow-up x-ray examination was ordinarily not made until 28 days after the start of treatment, the 37 day average does not represent the minimum figure. No correlation was found between the healing time and the age of the patient, size of the crater, history of previous recurrences, or duration of symptoms.

A difference of opinion exists among roentgenologists and internists regarding the interpretation of persisting deformity and irritability of the duodenal antrum. Some interpret the deformity as due to scar formation and others, especially if irritability is present, to persistence of the ulcer even when the crater has disappeared (116, 120, 121, 122). A small ulcer with duodenitis, as well as a scar, can produce deformity of the duodenal antrum, hence it is difficult to determine positively whether the deformity which persists for weeks after the disappearance of the crater and clinical symptoms is due to failure of the ulcer to heal completely or to the scar.

At any rate, it is well established that a duodenal or gastric ulcer under conditions of strict medical management heals rapidly in the majority of instances, and this is of great significance in the light of experimental observation on animals.

Thus when the healing time of an excision ulcer of the pyloric or duodenal mucosa of the dog is compared with the usual filling of a crater of a duodenal ulcer or of a gastric ulcer in man, the difference is not striking; similarly the healing time of an excision ulcer of the stomach of the rabbit on rough food is comparable to the filling time of the crater of a gas-

tric ulcer in man; and when a postoperative jejunal ulcer in the dog is protected from gastric contents, it heals within 30 days.

Comment

These observations indicate that in man and animal, under favorable conditions, acute and "chronic" ulcers heal at almost the same rate.

It is frequently stated that the scar tissue in the base of a chronic ulcer acts as an impediment in the normal healing process. According to the view presented here, the characteristic feature of a chronic ulcer, namely scar tissue, is the result of the chronicity and is not, to any marked degree, the cause of the failure to heal.

There are two differences between the healing of an excision ulcer in the dog and a "chronic" duodenal or gastric ulcer in man. *One* is that in most ulcer patients, "favorable conditions" are required for prompt healing; the *second* is that in some ulcer patients the lesion heals very slowly, and occasionally perforates or erodes a blood vessel, even under "favorable conditions."

Since a delay in healing of an acute ulcer causes its transformation to a chronic ulcer, and since the persistence of a chronic ulcer must be due to some factor or factors which prevent it from healing, it is important to investigate the factors which retard or facilitate healing to determine, if possible, what are the crucial elements in "favorable" or "unfavorable" conditions.

Factors Which Influence the Healing of an Acute Gastric Ulcer Produced by Excision or the Local Injection of Necrotizing Substances

A variety of methods have been used to produce ulcers for the purpose of studying the effect of some factor on their healing. For the present we shall consider only those experiments in which acute lesions were produced by local measures.

The following substances have been injected into the submucosa of the duodenum or stomach to cause a slough at the site of injection: 5 per cent silver nitrate solution (8, 9, 37, 42); ethyl chloride (32, 38); 1 per cent HCl solution (5, 14, 16, 40); 5 or 10 per cent formalin (31, 42); adrenalin (39, 42); nicotine (42); "neurine" (1); charcoal suspension (21); ferric chloride (37); and "gastro-toxic serum" (56). Acute ulcers have also been produced by cauterization with a hot iron (30, 33, 37, 47). It has been found that ulcers produced by these methods generally heal at the same rate as ulcers produced by excision. However, Nicolaysen (32), who produced ulcers by freezing an area in the anterior gastric wall of rabbits, o

served a failure of the ulcer to heal in some animals as long as six months after the operation.

Anemia

The early students of the problem of gastric ulcer were impressed by the clinical association of anemia with peptic ulcer during the active stage of the disease. Quincke (37) produced anemia by extensive hemorrhage in two dogs and found that the ulcers did not heal as rapidly as in two control dogs. Silbermann (41) and Litthauer (135) produced anemia in dogs by administering pyrogallic acid intravenously in a few experiments and came to the same conclusion. Fütterer (18) reported confirmation in rabbits. Zironi (136) presented some evidence indicating that gastric ulcers occur more frequently in anemic than nonanemic vagotomized rabbits. Gibelli (137) did not observe that anemia predisposed to delayed healing.

None of these reports provide sufficient evidence to warrant a definite conclusion although they tend to indicate that severe anemia predisposes to delayed healing and even to extension or perforation. More recent students of the problem of peptic ulcer have not specifically studied the matter, perhaps because of the fact that ulcers recur in patients in the absence of anemia and because of the clinical impression that healing proceeds rapidly after hemorrhage from the ulcer. However, Pollard et al. (107) concluded from their studies on the healing of gastric ulcer that anemia might have an adverse effect, and that further investigation of this question is desirable.

Acid

Litthauer (135), after producing anemia and an acute gastric ulcer in three dogs, gave them 0.37 to 0.5 per cent HCl solution daily. He also produced an acute ulcer, ligated the gastric vessels, and introduced acid into the stomach daily. The observations made do not permit a conclusion. Matthes (27) performed an experiment in one animal in which he produced an ulcer and to which 0.5 per cent HCl solution was given daily. He believed the acid caused delayed healing. Greggio (19) performed a few experiments similar to those of Matthes and came to the same conclusion.

The oral administration of hydrochloric acid once a day is not a satisfactory procedure because it does not simulate the more prolonged type of secretion present in some ulcer patients and the hypernormal acidity of the gastric contents associated with gastric retention. Bolton (56) attempted to avoid this difficulty by feeding food soaked in 0.5 or 0.6 per cent HCl. He produced acute ulcers in 24 guinea pigs and fed the acid diet to 12 and a normal diet to the remainder. He found no difference in the rate of healing of the ulcers in the two groups. When he fed an alkaline

diet (food soaked in 4 per cent sodium bicarbonate), a definite effect on healing time was not noted. However, when he administered an amount of gastrotoxic serum which alone was too small to produce an acute ulcer, the introduction of 0.2 per cent HCl or 0.5 per cent acetic acid solution would cause an ulcer to occur. He (141) also found that ulcers made in a Pavlov pouch healed as well when the pouch was arranged to cause retention of acid as when it was arranged to drain well. Dragstedt (8) made a similar observation.

The effect of injections of histamine on the rate of healing of acute ulcers has been studied on the hypothesis that the increased secretion of acid would delay healing. McIlroy (138) produced acute ulcers in the pylorus of seven cats and injected 10 to 20 mg. of histamine acid phosphate subcutaneously on alternate days. In eight control cats the pyloric lesion required 17 days to heal. In the cats given histamine, the initial lesion instead of healing in from 8 to 15 days had extended in six of the seven animals. Flood and Howes (14), using cats and dogs, interpreted their observations as indicating that the injection of 1 or 2 mg. of histamine twice daily interfered with the healing of prepyloric mucosal defects but not of defects in the mucosa of the cardia. Similar results were reported by O'Shaughnessy (139) and Carnot and co-workers (159); whereas negative results were obtained by Friedenwald, Feldman, and Morrison (16). Price (89) has recently shown that the administration of histamine in beeswax to dogs causes extension of surgical excision ulcers in the stomach. It should be remembered, however, that histamine has an effect on circulation as well as on the secretion of acid. Large doses are angiotoxic.

Gallagher (154) found delayed healing of ulcers of the duodenum after ligation of the pancreatic ducts in the dog. The delayed healing could be due to lack of neutralization of acid chyme or to a disturbance of nutrition secondary to a disturbance of intestinal digestion and absorption, or both.

Vagotomy and celiac ganglionectomy are said to have no influence on rate of healing (26).

The experimental evidence does not permit a conclusion that hydrochloric acid in the concentrations found in the stomach (up to 0.5 per cent) *alone* delays healing of acute gastric ulcers; this coincides with the results of clinical investigations (106). That acid is a contributory factor is definitely established by evidence cited elsewhere (pp. 217–221).

Mechanical Trauma

The effect of mechanical trauma on healing was studied (22) on ulcers 1.0 to 1.5 cm. in diameter, produced by the submucosal injection of silver nitrate in a pouch of the pyloric portion of the stomach. The ulcer was manipulated twice daily with bread crumbs, dry cotton, or the fingers for 10 to 15 minutes until marked congestion or some bleeding occurred. The

time of healing was increased from the control value of 15 to 20 days (10 ulcers) to 30 to 52 days (11 ulcers). Scar formation was definite, since lines of cicatrization were found. It was observed that the ulcers healed in such a manner as to reduce the exposure of the margins to mechanical irritation. The margins of the ulcer were markedly invaginated, so that the margin of the transition of mucosa to the base was protected.

Ferguson (11, 12) produced excision ulcers in the gastric mucosa of rabbits by a technique which left silk sutures in the base of the lesion, thus increasing connective tissue proliferation. When the animals were fed their usual rough diet, chronic gastric ulcer resulted.

Partial Pyloric Stenosis

The production of a partial pyloric stenosis introduces at least two and sometimes three factors. The two factors constantly present are prolongation of any mechanical and chemical trauma that might be present normally; the third factor is the loss of body weight which is rather marked in some animals.

Bolton (56) observed delayed healing in 10 cats with obstruction of the duodenum. Friedman and Hamburger (17), using dogs, observed delayed healing and a "chronic ulcer" in one animal at eight weeks. We (23) found delayed healing in five out of eight dogs; in the remaining three there was no loss of weight, indicating adequate evacuation of the stomach. Hughson (143) made acute ulcers on the lesser curvature of the pyloric portion of the stomach and observed delayed healing (up to seven weeks or more) in those animals in which the emptying time of the stomach was prolonged.

The uniformity of the results of these experiments and the availability of adequate control data show that partial pyloric stenosis delays healing, though it does not cause an ulcer to form spontaneously (142). The delay in healing is evidently due to a combination of prolonged mechanical and chemical trauma. It is difficult to assess the extent to which the loss of weight or disturbed nutrition contributed to the delay in healing.

Infection

Numerous clinical articles record that peptic ulcers recur or extend during the course of an infection. This has stimulated attempts to ascertain the local effect of infectious organisms on acute ulcers of the stomach.

Litthauer (135) failed to delay healing of artificial gastric ulcers by attempting to infect their edges. Others obtained similarly negative results (22, 39, 46, 109, 144). We (22) rubbed virulent streptococci and staphylococci into acute ulcers of the mucosa of a pyloric pouch and observed no greater delay in healing than that resulting from mechanical manipulation. We observed delayed healing of acute ulcers and definite evidence of chronicity in five dogs, cachectic due to intercurrent distemper or pancreatic duct

ligation, to which virulent streptococci were fed; but the chronicity of the ulcers was attributed more to the cachexia than to infection of the ulcer.

Askanazy (78) obtained chronic gastric ulcers of several months' duration in rabbits and guinea pigs by infecting acute lesions with *Oidium albicans*. Kotzareff and de Morsier (146) reported similar observations in dogs, pigs, guinea pigs, and rabbits. These cases of retarded healing could have been due to the slow healing of suture line ulcers in rabbits and the experimental conditions imposed on their animals, which may explain why Kirch and Stahnke (24, 25), using dogs, could not confirm this work.

Diet

Bolton (56) found that acute gastric ulcers in cats healed somewhat more quickly on a milk than on a meat diet. He explained this as due to the longer time meat remains in the stomach and the greater acidity of the gastric contents acting over a longer digestive period. He found more necrosis of the granulation tissue in the base of the ulcer of the meat-fed animals. It has been reported (104) that the feeding of glucose or lactic acid before and after the production of ulcers by cautery in rabbits had no significant effect on the rate of healing.

The marked tendency of the rabbit to develop a chronic ulcer when a piece of mucosa is removed and the serosa at the site of the lesion is closed with a silk or gut suture has been indicated previously. We (10) found that the ulcer healed in 30 days in 14 of 17 animals when a "soft diet," consisting of bread, milk, and cooked pureed carrots, was fed. In 12 control rabbits on their usual "rough diet," none of the ulcers had healed in 30 days. The *proliferation of connective tissue* in response to a suture (foreign body) is the chief factor in predisposing the rabbit to retarded healing or chronic ulcer in the presence of a rough diet; that is, two factors are required. However, this is not true of the ulcer which occurs in vagotomized rabbits (see p. 424).

Ligation of Blood Supply

Several authors have studied the effect of ligating the blood supply to the region of the stomach from which a piece of mucosa had been removed. One author (13) reported a delay in healing, whereas several observed no delay (6, 19, 135, 148). In our experience (105), ligation of all the gastric veins did not influence the rate of healing of an excision ulcer of the stomach in dogs. This procedure, however, markedly decreases the secretion of acid. When this is avoided by ligating only the blood vessels along the lesser curvature where the ulcer was produced, the ulcer also heals in normal time because of the anastomotic circulation. None of these expe-

ental attempts to study the effect of blood supply on the rate of healing an acute gastric ulcer simulates the decreased blood supply to the base a calloused ulcer. This could account for the slow healing of some gastric cers under strict therapeutic management. Also, much of the connective sue in a calloused ulcer has contracted to its limit at the time the man- ement is started.

Gastroenterostomy

Fibich (13) reported that an acute ulcer produced in the stomach of gs healed more rapidly when a gastroenterostomy was performed; this as not confirmed by Clairmont (6).

Morton (29) produced acute lesions in various portions of the stomach dogs with a gastrojejunostomy and diversion of the pancreatic juice to e lower ileum. The healing of the defect in the mucosa of the lesser curva- re was retarded whereas those of the greater curvature healed well. Such nimals frequently have a disturbance of nutrition due to defective intesti- al digestion, and manifest an abnormally prolonged secretory response to test-meal.

Matthews and Dragstedt (153) observed that the placement of a valve the pyloric canal to prevent enterogastric regurgitation delayed the aling of acute ulcers produced by silver nitrate in 6 of 13 dogs.

The effect of poor nutrition alone on the rate of healing of artificially roduced ulcers of the stomach or duodenum has not, to our knowledge, een reported.

Summary

(1) The evidence available does not warrant a definite conclusion that ither anemia or acid-pepsin in the concentrations found in the normal astric content, acting alone, delay the healing of artificially produced de- cts in the gastric mucosa. (2) The evidence indicates that the application f organisms directly to a defect in the gastric mucosa does not *per se* delay aling. (3) The ligation of the blood vessels directly supplying a region which a mucosal defect is made does not apparently delay healing. (4) Experiments have not been performed to ascertain whether the state of utrition or a systemic infection specifically delay healing of artificially roduced ulcers. (5) Mechanical trauma directly applied to an artificial lcer by rubbing the margins of the ulcer to the point of bleeding or by eding a rough diet in rabbits has been shown to delay healing. (6) Partial yloric stenosis, when it is sufficient to cause a definite delay in gastric vacuation, delays healing of an artificially produced ulcer. (7) A meat iet as compared to a milk diet delays healing in cats; the meat was not round and remained in the stomach longer than the milk.

It will be indicated later how the foregoing factors operating together, or with other factors, lead to the production of peptic ulcer. In the foregoing list the mechanical factor is the only one which when acting alone has been clearly shown to delay healing.

Attempts to Promote Healing of Acute Ulcers in the Gastric Mucosa

Various experimental attempts, besides the use of a milk and a soft diet cited above, have been made to increase the rate of healing of artificially produced lesions of the gastric mucosa.

There are reports which claim that the feeding of a suspension of silver chloride (35), of embryonic extracts (4), and of acetnaphthalene in oil (149), and that the injection of tryptophane (45) accelerate healing. It is claimed that the injection of histidine or lysine (45) and that vagotomy and celiac ganglionectomy have no effect on the rate of healing. The data submitted with these reports are not convincing.

Antacids

Dragstedt and Vaughn (9) produced an ulcer in the pyloric mucosa approximately 3 cm. in diameter by injecting silver nitrate submucosally and then placing 20 linen sutures through the mucosa and muscularis of the injected region. The gastric acidity was kept neutralized by the administration of alkalies from 6 A.M. to 11 P.M. In 10 untreated dogs, the ulcers had not healed at 25, 59, 90, 105, 6, 14, and 26 days in seven dogs, and had healed at 21, 74, and 76 days in three dogs. In 11 treated dogs, the ulcers had not healed at 7, 14, 38, and 50 days in four dogs, and had healed at 29, 12, 13, 99, 22, 33, and 42 days in seven dogs. Though not statistically significant, the result is definitely favorable. Bolton, as indicated above, failed to observe a definite effect of an alkaline diet on the rate of healing (p. 155).

As will be pointed out later, antacids and other procedures have been used to prevent experimental postoperative jejunal ulcer (p. 338).

Summary

A study of the process of healing of acute ulcers of the skin, stomach, duodenum, and jejunum reveals no significant differences. The reduction in the diameter of the ulcer by the contraction of the young connective tissue is a significant healing mechanism in ulcers of the skin and mucosa because regenerating epithelium will not bridge a gap much greater than 1.5 cm. across.

It is generally agreed that the healing process is the same in acute and chronic ulcers of the stomach and duodenum. The chronic peptic ulcer with the exception of the indolent ulcer, quite uniformly shows evidence o

an attempt to heal at some point in its margin. The cells of the foveolae of the margin of a chronic ulcer show marked proliferation. The base of the chronic ulcer presents a variable appearance, depending on the extent of chronicity. The nature of the base of the ulcer is usually the limiting factor in delaying healing, since epithelial cells will only grow over healthy granulation tissue and will not cover necrotic debris and avascular dense connective tissue.

Under ordinary conditions erosions and acute ulcers of the stomach and duodenum heal rapidly; in fact, so rapidly that it is remarkable that a chronic ulcer ever occurs. Defects due to denudation of the surface epithelium may be healed in a few hours. Erosions extending to the muscularis mucosae may be healed in two or three days. Acute ulcers measuring from 1.0 to 1.5 cm. in diameter usually heal in three or four weeks, an ulcer of the fundic mucosa healing more quickly than an ulcer of the pyloric mucosa, and the latter more quickly than an ulcer of the duodenal mucosa. The postoperative, "chronic" jejunal ulcer in the Mann-Williamson dog usually heals in 30 days, when placed under conditions favorable for healing.

The best evidence shows that so-called chronic gastric or duodenal ulcer will heal in from 14 to 100 days, average 40 days, under strict medical management. The true average is probably less than 40 days because of the infrequency of x-ray examination in arriving at the 40 day average.

These data on the rate of healing of acute gastric and duodenal ulcers in the non-ulcer-bearing subject and on the rate of healing of chronic peptic ulcer in the ulcer-bearing subject are biologically very significant. They show that the chronic peptic ulcer possesses almost normal potentialities for healing when placed under favorable conditions—for example, strict medical management. Since delay in the healing of an acute ulcer causes its transformation to a chronic ulcer, the question arises: What are the unfavorable conditions which prevent the ulcer from healing? or, Why does not an acute ulcer in an ulcer-bearing patient heal as rapidly as in a non-ulcer-bearing patient?

In animals it has been shown that acid contributes to a delay in healing; the same is true of gastric retention, and mechanical trauma due to rough food, particularly in the case of the stomach.

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CHAPTER 7

Summary

A circumscribed mucosal defect which penetrates the muscularis mucosae is an *ulcer:* one which does not is an *erosion.* A *peptic ulcer* is a benign, nonspecific ulcer located in those portions of the alimentary tract bathed by gastric juice.

The physiology of the secretion of acid, pepsin, and mucus by the stomach as well as the means for the regulation of the acidity of the gastric contents has been reviewed briefly. What is known regarding the secretion of Brunner's glands and certain important aspects of the motor activity of the stomach and duodenum have been briefly summarized.

The fact that common laboratory animals do not frequently develop chronic peptic ulcers spontaneously is advantageous in that it accords etiologic significance to a procedure which may cause an acute or a chronic ulcer. The fact that chronic ulcers may be produced in the subhuman species renders controlled etiologic and therapeutic studies possible.

The stomach does not digest itself when its circulation is adequate, when the tolerance of the cells to acid pepsin is not exceeded, and when the nutritional condition is adequate for the regeneration and proliferation of the cells of the gastric mucosa and for the secretion of mucus.

The intestine does not digest itself when its circulation is adequate, when the diluting, neutralizing, and buffering reactions between the gastric juice, Brunner's secretion, intestinal juice, bile, and pancreatic juice are maintained within the tolerance of the mucosa to acid-pepsin and active pancreatic juice.

All tissues other than the gastrointestinal mucosa appear to be subject to digestion by gastric juice secreted in ordinary amounts and concentrations. Impairment of the blood supply to any tissue, as well as the gastrointestinal mucosa, predisposes it to digestion by gastric juice secreted in ordinary amounts and concentrations.

A study of the process of healing of acute ulcers of the skin and gastrointestinal mucosa shows no significant difference. Under ordinary conditions erosions and acute ulcers of the stomach and duodenum heal rapidly.

Studies on the rate of healing of acute and chronic ulcers of the stomach and duodenum show that the chronic peptic ulcer of the ulcer-bearing patient possesses almost normal healing potentialities when placed under favorable conditions.

These facts raise certain basic questions pertaining to chronic peptic ulcer which will be considered in Part II.

PART II

On the Pathogenesis of Peptic Ulcer

The chapters in this part of the book will provide information bearing on the answer to the following basic questions: (1) What is the nature of the initial lesion which gives rise to peptic ulcer? (2) What are the causes of erosions and acute ulcers? (3) How do they develop? (4) Does a particular type of erosion or acute ulcer develop into a chronic ulcer? (5) What are the conditions under which erosions or acute ulcers develop into a chronic ulcer? (6) Why does peptic ulcer manifest a predilection for characteristic sites in the stomach, duodenum, and jejunum? (7) Does peptic ulcer manifest sex, seasonal, racial, age, and other differences in incidence; and, if so, why?

The methods used by different investigators for the production of ulcers will be presented and discussed. They cannot be presented so as to answer definitively in each case any of the specific questions raised above because, with but few exceptions, all the methods involve a multiplicity of mechanisms which must be evaluated for each method. Such a presentation is justified because several mechanisms operate abnormally in man to cause spontaneous gastric or duodenal ulcer.

OUTLINE OF CHAPTER 8

Histophysiology of the Acute Ulcerative Process

I. Introduction

II. Origin of the Ulcer

A. origin from some specific type of lesion as yet recognized

B. origin from an acute lesion

1. Coexistence of Acute and Chronic Ulcer
2. Acute Lesions in Infectious Processes
3. Acute Lesions in Burns
4. Occurrence of Chronic Ulcers at the Site of Predilect Acute Lesions
5. Chronic Ulcers Developing from Experimental Acute
6. Some Important Questions

III. Cause of Erosions and Acute Ulcers

A. outline of the mechanisms concerned in an ulcer process

IV. Anatomic Types of Ulcerative Lesions

A. preliminary remarks

B. primary necrosis of cells

1. Primary Necrosis without Interstitial Hemorrhage
2. Primary Necrosis Followed by Interstitial Hemorrhage

C. primary interstitial hemorrhage followed by necrosis

D. inflammation of lymphatic follicles, or "follicular ulcer"

V. Mechanism of the Production of Erosions and Ulcers

A. primary necrosis

1. Primary Necrosis without Subsequent Hemorrhage
2. Primary Necrosis Followed by Hemorrhage

B. PRIMARY INTERSTITIAL HEMORRHAGE FOLLOWED BY NECROSIS

1. Capillary Poisons
2. Occlusion of the Venules by Contraction of the Muscularis Mucosae
3. Generalized Passive Congestion or Capillary and Venous Stasis
4. Venous Occlusion and Thrombosis
5. Trauma
   a. Mechanical
   b. Chemical
   c. Caloric

C. COMMENT

D. WHAT NORMAL MECHANISMS MAY BE PERVERTED TO CAUSE VASCULAR DISTURBANCES?

1. Nervous Factors
   a. Vasomotor Control
   b. Motor Control
   c. Secretory Control
   d. Comment
2. Local Humoral Factors
   a. Histamine
   b. Acetylcholine

E. CAUSE OF THE FOCAL NATURE OF THE LESIONS

THE TYPE OF ACUTE LESION WHICH DEVELOPS INTO A CHRONIC ULCER

A. IN ANIMAL EXPERIMENTATION

1. Postoperative Jejunal Ulcer in the Dog
2. Pharmacologic Agents

B. IN MAN

SUMMARY

CHAPTER 8

Histophysiology of the Acute Ulcerative Process

Introduction

Some of the subsequent chapters of this part of the book will deal with the methods used by different investigators for producing ulcers. In almost every instance the procedure used could interfere with more than one of the several mechanisms responsible for maintaining the integrity of the mucosal cells. It is obvious that erosions and ulcers result from necrosis and that several mechanisms may be involved in the causation of the necrosis. This indicates that the formation of an erosion or an acute ulcer is probably never due to the effect of a single etiologic agent on a single mechanism for the preservation of the life of the cells in the mucosa. Therefore, some conception of the multiplicity of mechanisms which may be concerned is indispensable if the experimental observations discussed in the following chapters are to be evaluated properly.

Origin of the Ulcer

Cruveilhier (1), who in 1821 first described "erosions or hemorrhagic erosions," believed that all chronic peptic ulcers originated as acute lesions of the gastric mucosa. Rokitansky (2) expressed a similar opinion. Later, many observers came to consider chronic peptic ulcer as a separate disease, and gave little attention to the nature of the acute lesion. More recently, all students of the problem have favored the view that the chronic ulcer is initially either an acute ulcer or an erosion.

Thus, the two opposing hypotheses regarding the origin of peptic ulcer are:

1. A chronic peptic ulcer does not originate from any of the acute lesions seen in surgical and autopsy specimens of the stomach, duodenum, or jejunum.

2. A chronic peptic ulcer always originates from an acute lesion, which may be (a) any type of acute ulcer, or (b) only a certain type of acute ulcer.

Origin from Some Specific Type of Lesion as Yet Unrecognized

It is difficult to conceive, and no one has explained adequately, how a chronic ulcer could arise, like Minerva springing fully armed from the fore-

head of Jove, without its being initially an acute lesion of the mucosa. Even if an ulcer arose as a result of the alleged withdrawal of the trophic effect of nerve impulses on the cells of the mucosa, an acute lesion would occur. We may proceed, therefore, to an examination of the evidence in support of the assumption that a chronic peptic ulcer always arises as an acute lesion.

Origin from an Acute Lesion

Coexistence of Acute and Chronic Ulcer. Acute and chronic ulcers of the stomach and duodenum coexist. In 4,000 autopsies in Leeds, England, Stewart (3) found acute ulcers and erosions in the stomach in 2.93 per cent, and in the duodenum in 1 per cent. The German literature records an incidence of from 0.5 to 3.5 per cent (4). In Stewart's series of 117 cases of acute gastric ulcer, a single ulcer was present in 19 per cent, and in 48 per cent there were more than 12 ulcers. Acute ulcers of the duodenum are more frequently single, and it is rare to find more than 6 or 8. Two hundred forty-two autopsy specimens of gastric and duodenal ulceration included 89 cases of chronic gastric ulcer, with coexisting acute ulcer in 6.7 per cent, and 153 cases of chronic duodenal ulcer, with coexisting acute ulcer in 11.8 per cent.

The percentages may vary, but the coexistence of the two types of lesions has been observed repeatedly at autopsy, at operation, and by gastroscopy (19, 20). An acute ulcer may even be found extending from the border of a chronic ulcer of the stomach or duodenum (4, 6, 7); and an early chronic perforating ulcer may be found with old and recently healed ulcers and almost healed acute ulcers (4, 6, 7, 8).

None of the above findings constitute conclusive evidence, however, that the initial cause of the acute and chronic ulcers in a given patient was the same.

Acute Lesions in Infectious Processes. Acute ulcers and erosions may occur in the stomach and duodenum in acute and chronic infectious processes. At autopsy in such cases, acute, subacute, and chronic ulcers may be found (9–16). The cases reported are few, however, and the chronic lesions well may have been due to causes other than those underlying the acute ulcers.

Numerous cases have been reported (7) in support of the contention that a chronic ulcer may spread acutely or recur (17) in ulcer patients who develop an infection. This is a common clinical impression which has not been proved. (See Chapter 17.)

Acute Lesions in Burns. Extensive burns of the skin may cause erosions and acute ulcers in the duodenum and stomach. It has been suggested that chronic ulcers may arise from these lesions. Harkins (21) col-

lected 107 case reports in which an acute ulcer was found at autopsy in patients who had suffered burns. In 94 cases, the average time elapsing since the burn was 15 days; in only one of these (Cuthbertson, 1867) was the ulcer chronic—it was beginning to cicatrize six weeks after the burn—and in 31 the lesion was of the acute perforating type. In 13 cases in which a chronic ulcer was found from several weeks to several years after the burn, the ulcer was attributed to the burn; but in only three of these was the evidence for a relationship between the two lesions sufficiently impressive to be considered even presumptive. Thus, the contention that a chronic ulcer may develop from the acute ulcer which occurs with a burn is supported only meagerly.

Occurrence of Chronic Ulcers at the Site of Predilection of Acute Lesions. Acute lesions, exclusive of the small multiple hemorrhagic erosions or "fundus erosions" associated with toxic and infectious states, occur in the same regions of the stomach and duodenum in which chronic ulcers are found. This constitutes good circumstantial evidence when correlated with experimental evidence from animals.

Chronic Ulcers Developing from Experimental Acute Ulcers. Whereas none of the clinical observations clearly proves that a chronic ulcer originates as an acute ulcer, there is conclusive evidence that several types of chronic peptic ulcer produced experimentally arise from an acute lesion of the mucosa of the stomach or jejunum. This is particularly true of the chronic ulcer which occurs after excision of a piece of gastric mucosa in the rabbit fed a rough diet (22) and of the postoperative jejunal ulcer which occurs consistently in the dog after gastrojejunostomy and diversion of the pancreatic juice and bile into the lower ileum (23). (See Chapter 10.) It is also true of the ulcer caused by cinchophen, histamine, or caffeine.

Some Important Questions. Since no other hypothesis has any supporting evidence, the ensuing analysis necessarily is based on the assumption that chronic peptic ulcer in man starts either as an erosion or as an acute ulcer, and that a primary breach of the epithelial surface (mucosa) is therefore a *sine qua non* of a chronic ulcer. Proceeding from this premise the important questions to be considered in the problem of the genesis of chronic peptic ulcer are:

1. What are the causes of erosions and acute ulcers?
2. How do erosions and acute ulcers develop?
3. Does a particular type of erosion or acute ulcer develop into chronic ulcer?
4. Why does peptic ulcer manifest a predilection for characteristic sites in the stomach, duodenum, and jejunum?

5. What are the conditions under which erosions or acute ulcers develop into chronic ulcers?

Cause of Erosions and Acute Ulcers

Outline of the Mechanisms Concerned in an Ulcerative Process

It is possible in only a few instances to state definitely the more important mechanisms which have been disturbed when an erosion or ulcer has been produced experimentally. Hence, in outlining or classifying the mechanisms concerned in an ulcerative process, it is desirable to prepare as comprehensive an analysis of the possibilities as our present knowledge of the anatomy and physiology permits; then, in specific instances, it may be possible to eliminate hypothetic etiologic factors as the evidence permits, and to evaluate the relative importance of the remaining mechanisms.

The divisions of any classification of causes of erosions or ulcers overlap, since any theory of the ulcerative process is, because of the nature of the process, a multiple factor theory. For example, there are instances in which a single agent may produce, in the same stomach, erosions and acute ulcers which anatomically are quite different. We have prepared two outlines of the mechanisms which may be concerned in an ulcerative process. The first (Table 4) is as comprehensive as our knowledge permits. The second (Table 5) classifies the causes as (1) extrinsic and (2) intrinsic.

Table 4

A Hypothetical Outline of the Possible Etiologic Mechanisms Concerned in the Ulcerative Process

I. Vascular Disturbances (Internal and External Causes)

- A. Infarction, due to
  1. Embolism or thrombosis of arteries or veins, with or without primary changes in their walls.
- B. Spasm of Arteries, due to
  1. Vasoconstrictor nerves, toxic agents, or chemical, caloric, or mechanical trauma.
- C. Spasm of Muscularis Mucosae, due to
  1. Nerves, stimulating or toxic agents, or
  2. Chemical, caloric, or mechanical trauma, or asphyxia, causing
  3. Occlusion of arteries or veins, or both.
- D. Spasm of Muscularis Propria, due to the same factors as in C1 and C2, above, causing spastic motor effects in stomach and duodenum, as seen in
  1. Vomiting
  2. Asphyxia, or
  3. Reflex pylorospasm and gastrospasm, which may rupture or traumatize the capillaries.

E. Disturbances of Capillary Circulation, due to
1. Developmental defects, such as capillary tortuosity, or "vasoneurotic diathesis."
2. Stasis, secondary to low blood pressure, as in shock, disturbances of venous return, the action of vasodilators produced locally or present in the systemic circulation, or ingested irritants.
3. Capillary poisons.

F. Disturbances of the Coagulability and Filtrability of the Blood.
1. Increased coagulability, predisposing to thrombosis of arteries or veins, and
2. Decreased coagulability, predisposing to hemorrhage when the capillaries are traumatized by mechanical or chemical trauma.
3. Hypoproteinemia, predisposing to edema, which in turn may decrease blood supply and predispose to anoxia and lowered resistance to digestion.

G. Hypo- or Hyperactivity of the Endocrine Glands may predispose to
1. Vascular disturbances.
2. Spasm of the musculature.

II. Gastritis (Internal and External Causes)

A. Of Small or Large Areas of Mucosa, due to
1. Infection, and bacterial poisons.
2. Metabolic "toxins."
3. Extrinsic poisons (cinchophen).
4. Food, drinks, and ingested irritants.

III. Acid-Pepsin, or Gastric Juice (Internal and External Causes)

A. Excessive Secretion of Acid-Pepsin
1. Due to
(a) External factors, such as foods, drinks, and smoking, or
(b) Internal factors, such as nervous states, secretory hormone imbalance, or local inflammatory release of histamine.
2. Acting on
(a) A normal mucosa, or
(b) An abnormal mucosa.

B. Normal Secretion of Acid-Pepsin
1. Acting on an abnormal mucosa, or
2. Acting in the presence of inadequate protecting mechanisms (see V, below).

C. Retention of Gastric Secretion, due to
1. Motor disturbances, such as pylorospasm.

D. Abnormality in the Secretion of a Mucolytic Enzyme.

IV. Mechanical Trauma (Internal and External Causes)

A. Chronic Compression of the Abdomen, as in Kyphoscoliosis.

B. Blows to the Abdomen.

C. Rough Food.

D. Motor Drive of Gastric or Duodenal Peristalsis.

E. Spasm or Hyperperistalsis (see I, D, above).

V. Disturbances or Inadequacies of Protective and Reparative Processes (Internal and External Causes)

A. Inadequate Secretion of Mucus, due to
1. Exhaustion of cells.
2. Abnormality of mucus formation, resulting from the effect of circulation, nerves, nutritional factors, or liver on the manufacture of mucus, or a

3. Relative deficiency of mucus, resulting from excessive secretion of acid, or
4. Islands of intestinal mucosa in the "gastric pathway," which are more susceptible to gastric juice than gastric mucosa.

B. Inadequate Neutralization of Acid, due to
1. Inhibition of secretion of Brunner's glands by nervous or metabolic factors, or
2. Reduced secretion of Brunner's glands by inflammation or by destruction by a previous ulcer.
3. Inadequate secretion of pancreatic juice, bile, and succus entericus, and
4. Inadequate regurgitation into the duodenal antrum and stomach.

C. Deficiency in Repair or Growth, due to
1. A deficient diet, as of vitamins, proteins, and minerals.
2. Disease of organs, such as the liver, which may produce nutrients for the cells of the stomach and duodenum, and a general lowered resistance which may be associated with systemic disease or cachectic states.
3. Poor local circulation.
4. Inadequate production of cellular or circulating substances which promote repair after local trauma.
5. Hypo- or hyperactivity of endocrine glands, acting to change the metabolism of the cells.
6. Excessive connective tissue reaction, which reduces the circulation locally, or
7. Relative inadequacy, resulting from the effect of external factors, such as acid-pepsin, irritating or rough food, and spasm or hyperperistalsis, or vascular disturbances due to smoking and anxiety states.

D. Trophic Nervous Effects Which When Withdrawn Derange the Metabolism of Cells So that the Cells Degenerate.

VI. Displacements of Mucosa (Internal or External Causes)

A. Islands of Intestinal Mucosa in the Stomach (Lesser Curvature and Pylorus) due to
1. Developmental defects, or
2. Recovery of mucosa from gastritis.

B. Operations Which Divert Acid Chyme to Areas of Lower Resistance (Gastrojejunostomy).

VII. Specific Epithelial Cellular Necrosis, due to

A. Toxic Agent
1. Acting directly on the cells, or
2. On being excreted by the cells.

VIII. Constitutional and Psychosomatic Causes

This is a reiteration of factors listed above, because constitutional and psychosomatic factors must operate via the nerves or circulation to cause ulcers. To say that a disease is constitutional, psychosomatic, or hereditary does not always assist in the solution of the problem; it sometimes tends to retard. The following suggestions have been made:

A. Presence of Islands of Intestinal Mucosa in the Stomach.

B. Spasmogenic Constitution, or "Autonomic Imbalance," or Vagosympathiotonic Diathesis, indicating the claim that the autonomic system of the ulcer patient reacts differently from that of a non-ulcer patient.

C. Vasoneurotic Diathesis, referring to a spastic-atonic condition of the capillaries which causes tortuosity and predisposes to stasis.

D. Hypersthenic Diathesis, referring to a tendency toward hypertonus of the gastric musculature and hypersecretion of acid.
E. Low Alkalinity of Blood and Tissues.

Table 5

A Brief Classification of the Causes of Erosions and Acute Ulcers According to Extrinsic and Intrinsic Factors

I. Extrinsic Causes
- A. Deficient Diet.
- B. Irritating Diet.
- C. Ingestion of Organic and Inorganic Poisons.
- D. Bacterial Infections and Toxins.
- E. Acid-Pepsin.
- F. Gastric Motor Drive.

II. Intrinsic Causes
- A. Metabolic Poisons.
- B. Abnormalities of the Mucosa.
- C. Abnormalities of the Capillaries.
- D. Disturbances of Vascular Supply.
- E. Disturbances of Blood Coagulability and Filterability.
- F. Disturbances of Nerve Supply, affecting
  1. Metabolism of cells.
  2. Secretion.
  3. Musculature.
  4. Blood vessels.
- G. Disturbances of Endocrine Glands.
  1. Gastrointestinal hormones.
  2. General metabolic hormones.
- H. Disturbances of Other Organs.
  1. Those which manufacture nutrients for mucosal cells.
  2. Those required for the maintenance of resistance to injury, growth, and repair.

Anatomic Types of Ulcerative Lesions

Preliminary Remarks

A classification is presented of the anatomic types of acute mucosal lesions without regard to cause (Table 6); an etiologic classification according to the anatomic type of lesion would be too presumptive and involved, since two different anatomic types of erosions may coexist.

Table 6

Anatomic Types of Initial Lesions in the Gastrointestinal Mucosa

I. Primary Necrosis of Cells
- A. Without Subsequent Hemorrhage.
- B. With Subsequent Hemorrhage.

II. Primary Interstitial Hemorrhage Followed by Necrosis

III. Inflammation of Lymph Follicles, or "Follicular Ulcers"

In Chapter 1, an erosion was defined as a defect in the gastric mucosa which extends to, but does not involve, the muscularis mucosae and heals without a scar. Such an erosion may have blood or pigment in its margins or may have been preceded or followed by hemorrhage; this is, descriptively, a hemorrhagic erosion. When the erosion does not present evidence of preceding or subsequent hemorrhage, the lesion is described as an anemic or nonhemorrhagic erosion. In the latter case one cannot be certain whether the erosion was initially hemorrhagic or nonhemorrhagic in type unless the lesion was seen initially. The same applies to acute ulcers.

Bolton (7) introduces an etiologic viewpoint into his classification of erosions or "superficial ulcers." He believes that there is a definite difference between the processes which cause a "hemorrhagic erosion" and an acute ulcer, superficial or deep, which results from interstitial hemorrhage.

> The former is a superficial loss of substance in the mucous membrane of traumatic origin and of little importance, the hemorrhage being the essential feature. The latter, whether superficial or deep, is an acute ulcer due to digestion of a circumscribed portion of the gastric wall of the stomach by gastric juice. The ulcer is the essential feature and the hemorrhage only of importance because it has initiated the lesion . . . An "erosion" is of precisely the same nature as an "abrasion" of the mucous membrane produced by an injury inflicted by some external agent.

Langerhans (14) and Aschoff (29) recognized two types of erosions according to their size and location. The first type, frequently referred to as the "stigmata of Beneke," are small, punctiform, manifold, hemorrhagic erosions found in the mucosa of the corpus, particularly in the region of the greater curvature. He refers to them as "*fundus erosions*." The second type are relatively larger, fewer in number, and deeper than the first type, and are limited chiefly to the lesser curvature and the pyloric antrum and canal. He refers to them as *erosions of the gastric pathway*.

Sometimes the erosions follow the folds of mucosa. In fact, occasionally the hemorrhage into the mucosa and the hemorrhagic erosions may be in the form of streaks, several millimeters or centimeters long and a few millimeters wide. Again the hemorrhages may occur in patches or as ecchymoses and the area may be completely eroded or eroded only in circumscribed areas in a hemorrhagic or anemic patch. In the presence of anacidity and in very fresh specimens, petechial, ecchymotic, or streak-like hemorrhages may be found in the mucosa in the absence of an erosion. The different types of lesions are seen in the stomach and duodenum of man as well as of experimental animals. Hemorrhages into the mucosa, without erosion, indicate that the specimen is "fresh," or that there is an anacidity.

An erosion which has been studied from its inception and under direct

vision with histologic control is the erosion caused by the administration of caffeine in combination with histamine in the stomach of the cat. The erosions observed occurred in the pyloric mucosa within five hours after the first administration of the drugs. Two types of lesions resulted and sometimes coexisted in the same stomach; namely, a primary anemic necrosis and a primary hemorrhage followed by necrosis. The latter type of lesion is most commonly seen.

The three anatomic types of acute lesions will be described in relation to the initial process which appears to be concerned in their production.

Primary Necrosis of Cells

This expression refers to necrosis of the mucosa in which interstitial hemorrhage is not a primary event. Instead the tissues are anemic and hemorrhages may or may not occur secondarily.

Primary Necrosis without Interstitial Hemorrhage. When this type of lesion occurs during the action of caffeine and histamine on the cat's stomach, and under direct vision, a blanched area is evident as is shown in figure 39. The area becomes eroded in the center and the anemic edges become elevated. The section shown in figure 40 was made at the edge of the erosion indicated in figure 39, and shows relatively normal mucosa adjacent to anemic mucosa, the edge of the erosion which has

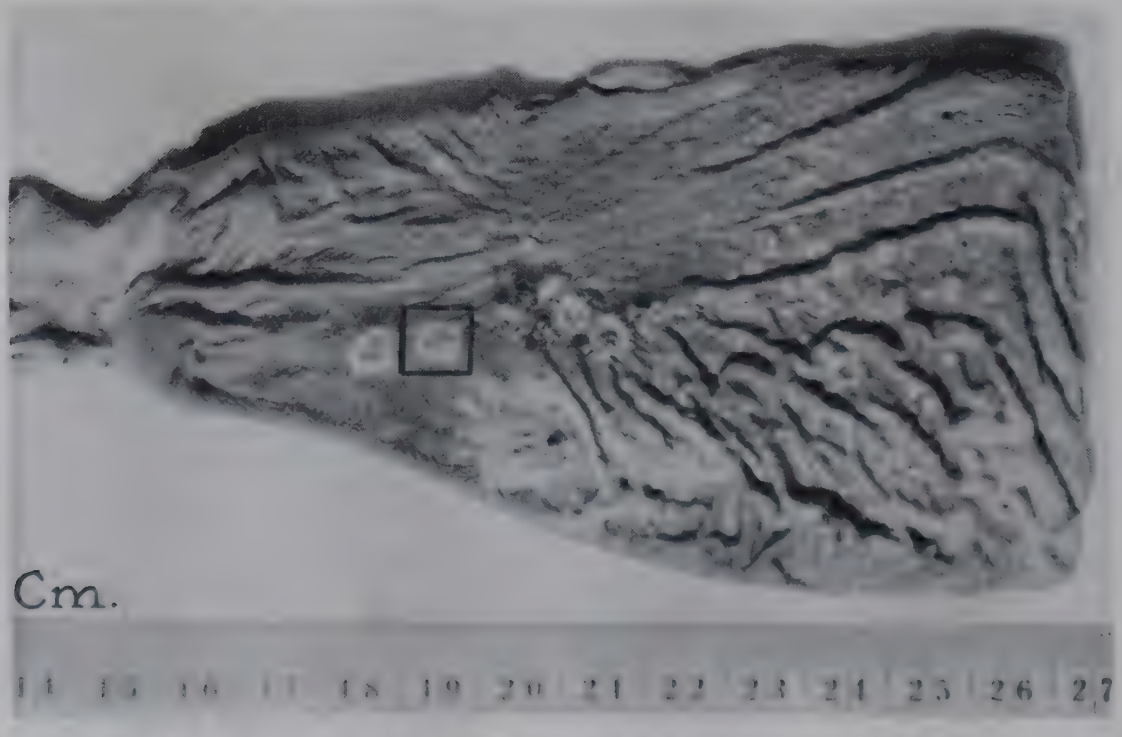


Fig. 39. Multiple diffuse areas of superficial desquamation of the mucosa in a cat. Produced in the course of a study on gastric secretion in an acute experiment of five hours duration. The animal received a total of 3.75 mg. of caffeine sodium benzoate and 0.6 mg. of histamine dihydrochloride.

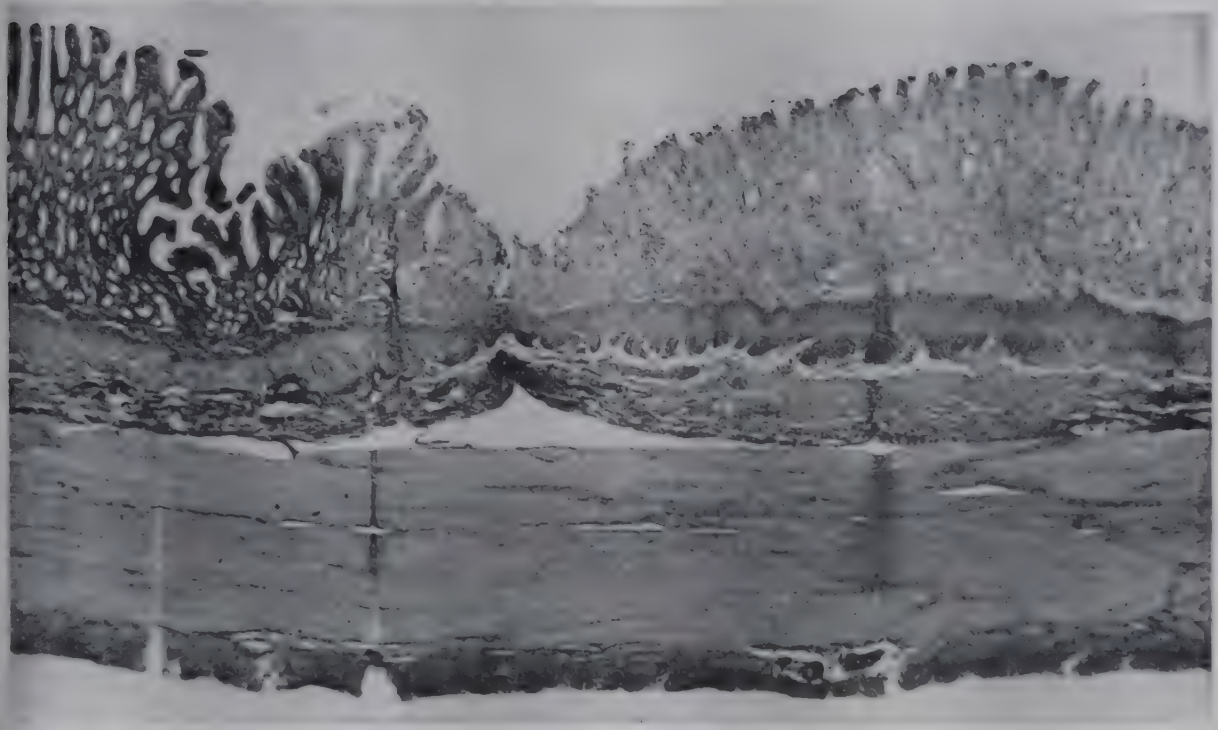


FIG. 40. Photomicrograph showing erosion of gastric mucosa and desquamation of the glandular epithelium, swelling of collagenous fibers and edema of interstitial tissues of mucosa and submucosa. (Courtesy, Roth and Ivy: *Gastroenterology*, **2:** 274, 1944.)

entered the muscularis mucosae, with a small area of hemorrhage present, and then the anemic and swollen mucosa (24). The entire thickness of the mucosa in the involved area is anemic and manifests interstitial edema, but the erosion begins from the surface and extends toward the muscularis mucosae. No evidence of thrombosis of underlying vessels has been observed early during the development of these ulcers; however, after the ulcer has penetrated to the muscularis mucosae, then thrombosed vessels are found (24). The thrombosis may be due to the action of acid on the blood vessel wall, and is probably not primary.

Other erosions of this type have been described but have not been seen to occur under direct vision.

Rosenow (25), in describing acute ulcers produced by the intravenous injections of streptococci, says that "in some instances the ulcer forms without a preceding hemorrhage, in circumscribed grayish swollen necrotic areas." Similar lesions have been seen by other investigators who injected bacteria or toxins, such as diphtheria toxin (26).

Simonds (27) has described necrosis of the mucosa without a primary hemorrhage or congestion in dogs given cinchopen. The smallest ulcers "involve the tips of single villi." "The stroma of the villus is infiltrated with polymorphonuclear leucocytes and the epithelium of the top of the villus is absent." A wisp of exudate may be found to issue from the ulcer through

the defect in the epithelium like smoke coming from a chimney. Focal lesions may be found at any depth in the mucosa ranging from a local edema to a frank abscess with complete liquefactive necrosis of the gastric or duodenal glands, or to a draining fistula-like ulcer. Thus, in this case a definite gastritis precedes the formation of the ulcer.

Primary Necrosis Followed by Interstitial Hemorrhage. Bolton (7), who used a gastrotoxic serum for producing erosions and acute ulcers, presents sections and other evidence indicating that in some instances the formation of the ulcer is preceded by a noninflammatory necrosis which is followed by hemorrhage. He states,

> the patches are primarily necrotic, and not inflammatory. The process evidently begins on the free surface, and extends towards the base of the glands, because all transitions can be seen from a mere superficial necrosis to a lesion which extends to the muscularis mucosae. The dead tissue is sharply marked off from the living, and no initial change can be seen in the cells at the margin of the necrosed area. No thrombi agglutinated corpuscles are seen.

These lesions later become infused with blood and stained black by altered blood pigment. The necrotic tissue disappears after 48 hours and leaves a punched-out ulcer with a clean base. The process starts at the surface and may extend to or through the muscularis mucosae. A similar process has been described as a result of the administration of bacterial toxins and other toxic substances.

If such an erosion is studied after the necrotic debris has been digested or has sloughed, it obviously cannot be determined whether the ulcerative process was due to a primary necrosis with or without hemorrhage, or to a primary hemorrhage followed by necrosis.

There is no direct evidence based on a series of observations on the same lesion showing that primary necrosis followed by hemorrhage actually occurs. However, when several lesions in the same stomach are studied, as has been done by Bolton and many others, presumptive evidence is obtained indicating that primary necrosis followed by interstitial hemorrhage and hemorrhage into the stomach actually occurs as a type of ulcerative process.

Primary Interstitial Hemorrhage Followed by Necrosis

This expression refers to a lesion in which an interstitial hemorrhage occurs as a primary event and is followed by necrosis and the formation of an erosion or acute ulcer. This is the most common type of lesion which results in the formation of an erosion or an acute ulcer.

The process which leads to interstitial hemorrhage and the formation of an erosion has been followed by direct vision and histologic sections during the course of five hours in the cat's stomach treated with caffeine and

histamine, given parenterally (24, 30). The gastric mucosa first becomes hyperemic and then cyanotic. During this transition the mucosa becomes swollen and succulent and the rugae fuller and smoother. Bleeding is easily induced by minor trauma. In the stage which precedes cyanosis and during the cyanotic stage, the vessels are engorged with blood. This is particularly true of the veins which lie vertically in the stroma of the mucosa between the glands. The veins at the base of the mucosa and external to the muscularis mucosae as well as those in the submucosa are engorged. Red blood cells and transudate are found in the interstitial tissues in areas. The areas in which numerous erythrocytes are found in the interstitial tissue when viewed from the surface appear as petechiai or ecchymotic hemorrhages in the mucosa. In from three to five hours, and in the presence of highly acid gastric juice, these hemorrhagic areas are digested, leaving punched-out or ragged erosions.

Two types of erosions result. The much more common type is the ordinary *hemorrhagic erosion*, described so many times by pathologists, with a black to dark red margin and base due to staining with blood or blood pigment (acid hematin). The second type is an erosion which is no longer discolored with blood, because the extravasated blood and necrotic tissue have been digested entirely without hemorrhage occurring from the blood vessels in the surrounding, more or less edematous, tissue. It is a *nonhemorrhagic erosion* which was associated with or due to a primary interstitial hemorrhage. These erosions due to primary interstitial hemorrhage may or may not be associated with a thrombosis of the veins. It cannot be stated, however, whether the thrombosis is primary or is secondary to the exposure of the vessel to acid gastric juice.

Wolf and Wolff (31), observing under direct vision the gastric mucosa of a patient with a gastric fistula, have reported that

> intense anxiety, hostility, and resentment were accompanied by severe and prolonged engorgement, hypermotility, and hypersecretion of the stomach. In this state mucosal erosions and hemorrhages were readily induced by even the most trifling traumas and frequently bleeding points appeared spontaneously as the result of vigorous contractions of the stomach wall.

In their patient hemorrhagic erosions occurred when the mucosa was congested with blood.

Rosenow (25), who injected streptococci intravenously into animals, wrote that

> a primary lodgement and growth of bacteria . . . [occurs] . . . in the interstitial tissue of the glands and between the cells, followed by hemorrhage, necrosis, and ulceration. . . . The loss of tissue usually begins in the center of the hemorrhagic infiltrated and necrotic area as early as 18 hours after injection.

Rosenau and Anderson (32), after the subcutaneous injection of diphtheria bacilli or diphtheria toxin in guinea pigs, noted sharply defined areas of congestion of the mucosa in the region of the pylorus and duodenum 24 hours after the injection. Later, well-defined interstitial hemorrhage with erosion and acute ulcers, sometimes extending to the muscularis, were found.

When the hemorrhage is well defined it is wedge-shaped, the surface epithelium being the base of the wedge. The point of the cone or wedge sometimes reaches the muscularis mucosae and may penetrate it.

Hart (5), however, regarded vasospasm or vasoconstriction as the essential underlying factor in the pathogenesis of the acute ulcerative lesion. If prolonged, the resultant ischemia leads to necrosis, followed by hemorrhage; if brief—that is, if the ischemia is terminated before digestion of the ischemic area occurs—the subsequent compensatory vasodilatation and stasis result in extravasation of blood, producing a focal hemorrhage. The only type of evidence which could sustain such a hypothesis would be direct observation of the gastric mucosa while the disturbing factors are operating. Hart did not submit any evidence, and our observations do not support him.

Many investigators have observed lesions of the various types referred to above after injecting various bacteria and organic and inorganic poisons, after chemical and mechanical trauma of the mucosa, or after the administration of drugs or the stimulation of the vagi which causes spasm of the gastric musculature, or in death associated with "shock." In most instances congestion followed by interstitial hemorrhage, erosion, or acute ulcer have been observed; in others necrosis with or without hemorrhage, or inflammation with focal areas of inflammation or necrosis, as described above for cinchophen, suggesting that the poison is being excreted, have been observed. The literature leaves no doubt but that the same poison may produce either primary hemorrhage or primary necrosis.

Inflammation of Lymphatic Follicles, or "Follicular Ulcer"

Lymphoid follicles without a capsule are found in the gastric mucosa. They are situated at the base of the glands and superficial to the muscularis mucosae. The base of the follicle usually lies on the muscularis mucosae and its apex extends toward the surface. The follicles are found throughout the stomach, but are concentrated along the lesser curvature, particularly of the pyloric region. After puberty they decrease in size and number; after the age of 40 they are found almost only in the pyloric mucosa (12, 33, 35).

Cruveilhier (34) first described ulcers due to inflammation of the

lymphoid follicles. Others have similarly described gastric ulcers due to inflammation of these follicles in tuberculosis, typhoid fever, diphtheria, and other infectious conditions (13, 39–47).

Fox (48) has described the ulcerative process as follows: the enlarged follicles appear on the surface of the mucosa as small (1–2 mm.) elevated white areas, giving the appearance of a mass beneath the surface of the mucosa. Histologically, the follicle is enlarged and hyperplastic. The blood vessels about it are engorged; the adjacent tissues are infiltrated with round cells. As the follicle enlarges, its center becomes necrotic and the overlying mucosa gives way, probably due in part to pressure necrosis. This is the acute "follicular ulcer." When the ulcer is recent, it is identified by the round cells in its margins and base and the overhanging margins which tend to hide the ulcer. When exposed to digestion, the round cells may not be present.

Though there is no reason to doubt that the lymphoid follicles of the gastric and duodenal mucosa may be involved in the ulcers found in patients with tuberculosis and typhoid, it is unlikely that the follicles are primarily involved in other types of ulcers. Rosenow (25), in his work on streptococci, which he believed had a special affinity for the gastroduodenal mucosa, found only four instances in which the ulcer may have been equivocally due to a primary infection of the lymph follicles. Others who have produced acute ulcer and erosions by the injection of bacteria either overlook or do not emphasize a primary infection of the lymph follicle as a cause of the ulcers seen.

Some years ago, Cole (12) proposed that gastric ulcers start as a localized abscess in the wall of the stomach, ultimately rupturing into the lumen. This "boil conception" of the pathogenesis was based essentially on three arguments, viz.: (1) Radiologically, gastric ulcers usually are seen to decrease in size, very rarely to increase, (2) the edges of an ulcer are often undermined, and (3) the oldest connective tissue is found at the edges, not at the center as would be expected if the ulcer were constantly being enlarged by corrosion. No evidence has been advanced in support of this hypothesis. Ulceration has been found at operation and at necropsy in all stages from the smallest erosions to complete perforation, but discrete intramural abscesses have not been described. Smithies (9) was not convinced that gastric ulcer arises as a mucosal lesion because mural scars are often found in the stomachs of patients in whom peptic ulcer had never appeared. The fallacy of this reasoning is obvious.

Having described the various types of acute lesions which are seen in the stomach and duodenum, it is appropriate to consider the mechanism of their production. However, the mechanism of the production of a "follicular ulcer" is clear.

Mechanism of the Production of Erosions and Acute Ulcers

In considering the mechanism of the production of erosions and acute ulcers, it is important to keep in mind the anatomy of the blood supply of the mucosa (Fig. 41). It should also be kept in mind that the parietal cell susceptible to anoxia (64), and especially so to a decreased circulation a occurs during a fall of blood pressure. An erosion or acute ulcer is formed as a result of the sloughing or digestion of necrotic or damaged tissue. I acid is not secreted, an interstitial hemorrhage can occur without th formation of an erosion or ulcer, or necrotic tissue can persist for some tim *in situ* before sloughing and producing an erosion or ulcer. A localiz passive congestion or occlusion of the blood supply of the mucosa may

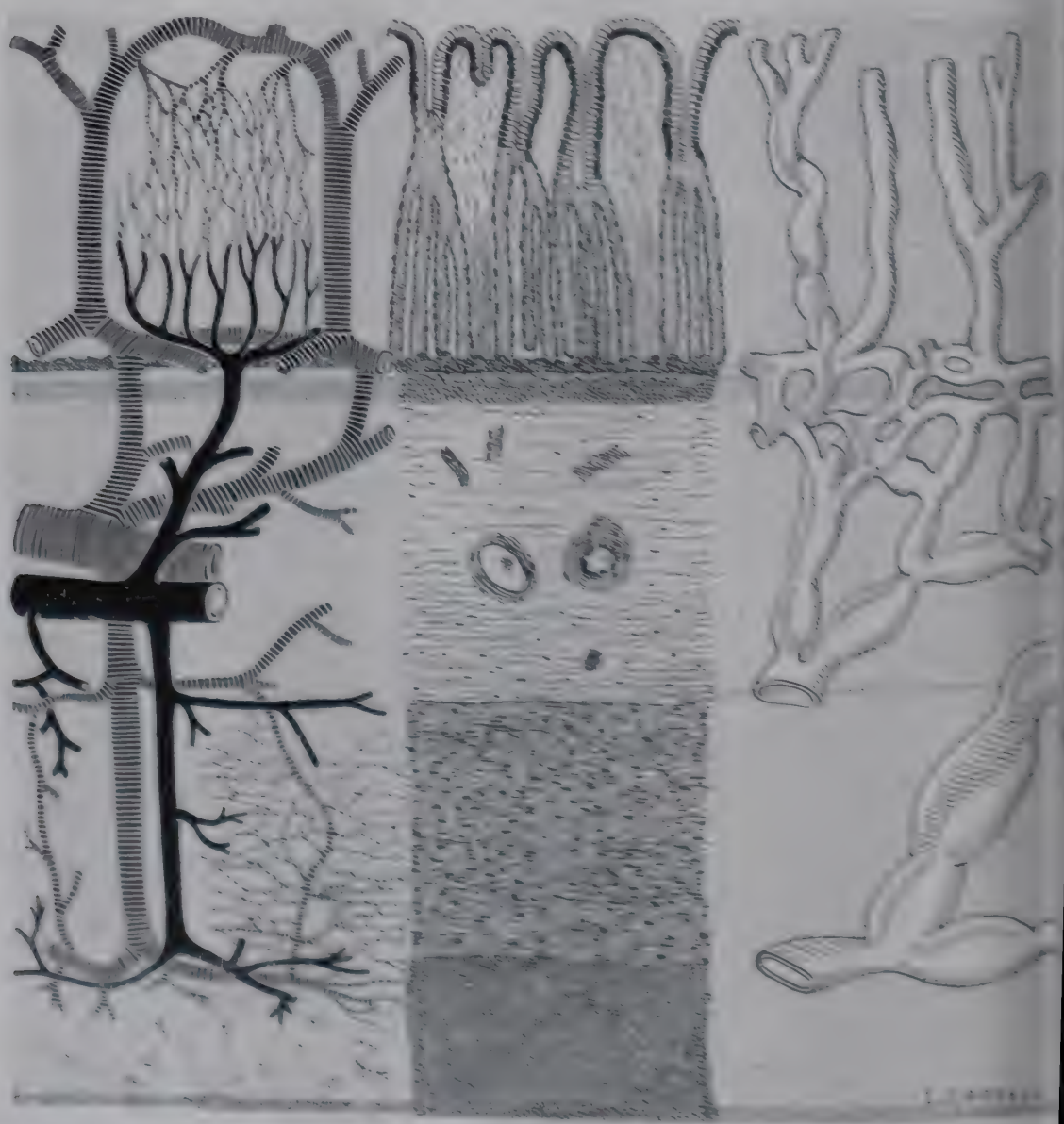


FIG. 41. The blood (*left*) and lymph (*right*) supply to the stomach in relation to anatomy of the stomach wall (*center*). (Redrawn from Mall.)

ese occur in the fundus or in the pylorus without interfering with the etion of acid.

Primary Necrosis

Primary Necrosis without Subsequent Hemorrhage. To obtain an of anemic necrosis, erythrocytes must be excluded from the part. would seem necessary for the arterioles to be closed to the passage of hrocytes and the venules and capillaries to be cleared of erythrocytes. he arterioles were constricted so that erythrocytes could not pass but ma could, then the area could be devoid of erythrocytes and local ma could or could not occur depending on the permeability of the illaries. If the arteries alone were completely constricted, the blood ent in the capillaries before constriction of the arterioles could tinge damaged mucosa. Hence, either "plasma streaming" or some mecha- for emptying the capillaries and venules of erythrocytes must occur rder to account for anemic necrosis. There are three ways that this be accomplished:

1. If the muscularis mucosae, through which the arterioles and venules more or less vertically, should contract sufficiently to occlude the od flow, it would seem that the venules should be occluded before the rioles because of the pressure gradient from arterioles to venules. It is robable that the muscularis mucosae may constrict to the point of nitting the passage of plasma without preventing the washing out of hrocytes from the capillaries and venules.

2. The arterioles may constrict, first, to an extent that permits the age of plasma only, and then in some instances to an extent which ws no blood to pass.

3. The arterioles may constrict, and then, as in Raynaud's disease, the illaries and venules may constrict. Either the venules must constrict his instance or the muscularis mucosae must constrict to prevent the flow of venous blood from the veins of the submucosa.

When these lesions are examined grossly and microscopically, the mic area is larger than the necrotic or eroded portion (Fig. 40). The ders of the necrotic or eroded area are edematous but contain no hrocytes, indicating that plasma streaming has occurred in the vessels ounding the necrotic or eroded area. Beyond the anemic area the els may be normally filled or congested. In such areas we have not d a thrombosed vessel unless the vessel has been exposed to gastric e. Rosenow (25) does not report observing thrombosed vessels, though did observe that the streptococci may occlude the superficial capil- s. (See Bolton (7).) It cannot be stated whether the anemia of the persists longer than 60 minutes, or whether its margins and base

become hemorrhagic later. It is reasonable to presume that the ulcer becomes hemorrhagic later, unless blood flow is suppressed by the edema of the margins and base of the ulcer.

In an anemic area, particularly when exposed to gastric juice, it is difficult to prove, even when anemic necrosis is produced by a potentially



FIG. 42. Diagrammatic representation of the mucosal and submucosal circulation as it occurs in man, rabbit, mouse and bat. Arteries black; veins white. The arteriovenous short circuit is located near the tip of the villus. The blood is directed through the central vein of the villus simultaneously with the spasm of the other terminal branches of the submucosal arteriole. These are located in the submucosa and are indicated by circles at their point of origin. Modified from Spanner. (Courtesy, Klemperer et al., *Am. J. Digest. Dis.*, 7: 412, 1940.)

toxic substance such as caffeine and histamine or other organic and inorganic toxic substances, how much of the necrosis is due to ischemia and how much to cellular damage caused by the toxic agent.

It is possible that spasm, due to nervous or toxic agents, may occur in the arterioles of the submucosa. This would occlude the blood supply

of the overlying mucosa. In this connection the observation of Spanner (59) on the vascular system of the intestinal villi, which are present in the duodenal antrum as well as the jejunum, should be mentioned. In man, rabbit, rat, mouse, and bat (Fig. 42) the arterioles supplying the villi arise at a right angle from the artery in the submucosa. They pass to the tip of



FIG. 43. Diagrammatic representation of the mucosal and submucosal circulation as it occurs in the dog and cat. Arteries black; veins white. The arteriovenous anastomosis is located in the submucosa. The other terminal branch of the submucosal arteriole which goes into spasm supplies the villus and is indicated by a circle at its point of origin. Modified from Spanner. (Courtesy, Klemperer et al., *Am. J. Digest. Dis.*, **7**: 412, 1940.)

the villi where they divide into two branches. One branch connects with the vein to form an arteriovenous shunt which closes to increase the blood flow through to the capillaries. In the dog, cat, pig, and horse (Fig. 43), the arteriovenous shunt is in the submucosa just proximal to the point where the arteriole of the villus arises. If such a mechanism exists, it must be con-

trolled either by a nervous or chemical factor, or perhaps by direct mechanical stimulation. It would appear to be important to know more about this mechanism and its control.

In the case of the gastric mucosa, a mechanism for an arteriovenous shunt has not been described. According to Djørup (65) and Disse (66), the arteries after piercing the muscularis mucosae enlarge and give off a number of ascending, more or less vertical, branches (Fig. 44). They view these arteries as being "end-arteries." One of the arteries which pierce the muscularis mucosae supplies 4 sq. mm. of mucous membrane, and 25 supply 1 sq. cm. Disse (66) finds the arteries to be spiral in their course in the empty or contracted stomach and to be straightened out in the digesting or distended stomach. When the arteries are straightened, there is less resistance to blood flow. In this way, rather than by arteriovenous shunting, he explains differences in vascularity in the digestive and interdigestive periods. To obtain an anemic necrotic area 1 cm. in diameter, it would appear that either a submucosal artery must become spastic, or its branches occluded by a local spasm of the muscularis mucosae. Another possibility should be considered when a toxic agent is injected; namely, that the submucosal artery supplying an area is wider open than others at

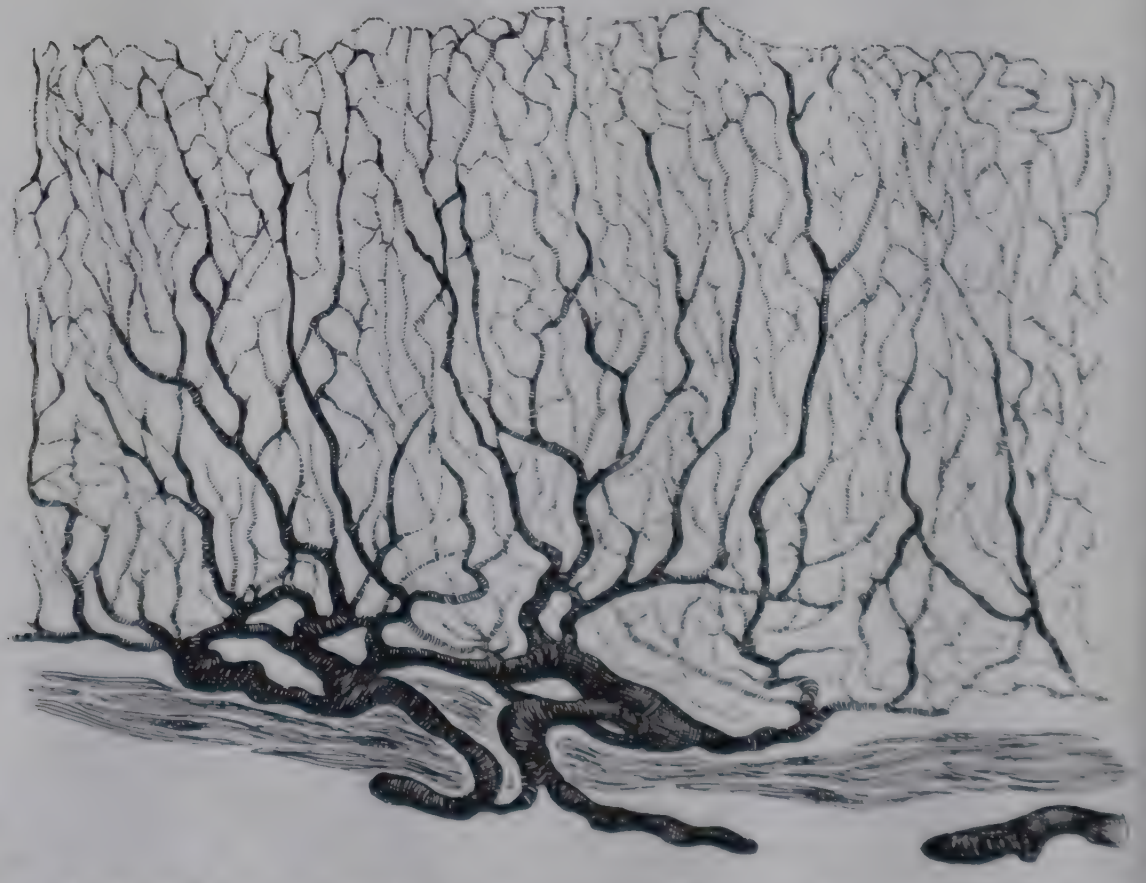


Fig. 44. Arterial supply to the gastric mucosa. (Redrawn from Djorup, *Ztschr. f. Anat. u. Entwicklngsgesch.*, **64:** 279, 1922.)

the time the agent reaches the stomach, and hence the branches of the artery and the cells it supplies are exposed to a larger dose of the agent. This is the usual explanation of the focal manifestations of a circulating toxic agent, though it is not the only explanation, since the susceptibility of the cells in one area may differ from that of another.

Primary Necrosis Followed by Hemorrhage. Though anemic infarcts occur in such organs as the extremities, the kidney, the spleen, and sometimes the heart, they rarely occur in the gastrointestinal mucosa. Into the necrotic border of anemic infarcts as they occur in various organs, erythrocytes infiltrate. It is reasonable to presume that an erosion due to anemic necrosis may become hemorrhagic later, unless the blood flow is suppressed by the edema of the margins of the defect. If an area of primary necrosis could be caused by a spasm of the arterioles and venules, it is reasonable to presume that, as in Raynaud's disease, after the cessation of the spasm the vessels might become congested and bleeding occur from damaged vessels.

Primary Interstitial Hemorrhage Followed by Necrosis

Hemorrhages into the mucosa can be produced by many procedures and agents. In only a few instances is the specific mechanism precisely known. In considering the possible mechanisms it is necessary to consider only the vessels of the mucosa, because all the large arteries, veins, or both, supplying the stomach may be tied without causing interstitial hemorrhage. If the stomach is traumatized during the operation in which all the large veins are tied, then hemorrhage into the mucosa and resultant death of the animal occurs.

Interstitial hemorrhage could result from (a) a capillary poison, (b) an occlusion of the venules by contraction of the muscularis mucosae, (c) generalized passive congestion, or capillary and venous stasis, (d) venous occlusion and thrombosis, and (e) chemical, mechanical, and caloric trauma.

Capillary Poisons. Though we suspect that all poisons either directly or indirectly injure the capillaries and may produce defects in their walls to the point that interstitial hemorrhage occurs, it is at present presumptive to draw such a conclusion. For example, cobra venom, which causes hemorrhage into the mucosa of the stomach and duodenum, commonly is stated to be a capillary poison. But Essex (50) points out that the assumption that the disturbances caused by cobra venom are all due to a single mechanism amounts to an oversimplification of the problem. In addition, when the stomach and intestine are acutely asphyxiated, asphyxial contractions may occur and rupture capillaries distended with blood which would not otherwise rupture.

Hagemann (51) presumptively explains the two general types of erosions referred to above as follows. He suggests that the more superficial hemorrhages found chiefly in the fundus are due to hemorrhage from the venous capillaries which open into the vertical veins and pass through the muscularis mucosae, and that the deeper and irregular-shaped hemorrhages which are less numerous are due to a lesion of the arterial capillaries. The latter, he suggests, are the result of toxic and bacterial action or arterial occlusion which is less likely to cause hemorrhage, or so many hemorrhagic areas.

Occlusion of the Venules by Contraction of the Muscularis Mucosae. This mechanism is easy to visualize but difficult to prove. The muscularis mucosae has not been stimulated by a needle electrode in an area to ascertain the effect of the contraction on blood flow. Even then, the possibility that the change observed by the stimulation was due to contraction of the blood vessels would have to be ruled out. Lichtenbelt (52) particularly has argued that spasm of the muscularis mucosae occludes the arterioles and causes an anemic necrosis which later may be followed by hemorrhage.

Generalized Passive Congestion or Capillary and Venous Stasis. All hemorrhages into mucosa which have been observed to occur by direct vision, except those due to direct mechanical trauma, have been preceded by congestion of the mucosa. In the presence of gastric juice, the anoxia due to a passive congestion of an area of mucosa should predispose to autodigestion to almost the same extent as ischemia of an area of mucosa due to arterial spasm.

When interstitial hemorrhages are produced in the stomach of the cat (30) by the slow intravenous administration of caffeine sodium benzoate (250 mg.), an active hyperemia is the first change observed in the mucosa. The rugae become smoother and larger. Cyanosis then appears. This is associated with capillary and venous engorgement, transudation, and the appearance of erythrocytes in the interstitial tissues. No evidence of arterial spasm or contraction of the muscularis mucosae was detected. When histamine is injected into cats at intervals to maintain a brisk secretion of gastric juice, the mucosa becomes hyperemic; the same is true of man (31). The doses used were not sufficient to cause a hypotension, which would predispose to cyanosis. In the experiments of five or six hours' duration, neither caffeine nor histamine alone caused hemorrhagic erosion, but when given in combination hemorrhagic erosions occurred. The histamine converted the minor hemorrhages to major hemorrhages and increased the rate of gastric secretion; at the same time gastric motility was increased.

Though caffeine acts on the vasoconstrictor center, its peripheral vaso-

dilator action predominates (53). Extensive vasodilatation can lead to stasis and injure the capillaries to the point that transudation and hemorrhage result. Small doses of histamine increase blood flow as judged by the reddening of the mucosa, though direct measurements on the circulation of the stomach *in situ* have not been made (54). Larger doses, particularly those which cause "histamine shock," undoubtedly cause capillary stasis and infiltration of blood into the mucosa (18, 36, 55). Some experimental evidence suggests that histamine causes contraction of arterioles and venules under certain circumstances, but such effects have not been demonstrated for the gastric mucosa. Thus, it is evident that histamine and caffeine, through an additive action, should predipose to interstitial hemorrhage.

Another possibility relative to the role that histamine may play in the cause of interstitial hemorrhage must be considered. Histamine is present in the gastric mucosa and there is evidence showing that histamine is released by tissues when they are damaged. Injury due to capillary stasis caused by caffeine may cause the local release of histamine which would increase the capillary stasis caused by caffeine (56). Histaminase is not found in gastric mucosa; whether it is present in the duodenal antrum is unknown.

Venous Occlusion and Thrombosis. A contraction of the muscularis propria or the muscularis mucosae could conceivably cause occlusion of the venules draining the gastric mucosa. This would decrease the resistance to digestion and predispose to hemorrhage.

Very little information is available regarding the physiology of the muscularis mucosae. The response of the muscularis mucosae of the intestine of the cat to drugs has been studied (57, 58). The more pertinent observations show that epinephrine, pilocarpine, pituitrin, and nicotine cause contraction, and that nitrates, cocaine, morphine, and atropine are depressants. The former drugs when given in relatively large doses cause interstitial hemorrhage and erosions of the gastric and intestinal mucosa. But these drugs have effects other than those on the muscularis mucosae.

If thrombosis of the veins of the mucosa or of the submucosa should occur in a localized area, this could cause a passive congestion of the area. Primary or uncomplicated thrombosis of these veins has not been reported.

The venous return from the stomach and intestine can be partially occluded by an intralumenary pressure of 10 to 20 cm. of water sustained for a period of 12 to 24 hours. Under such conditions focal necrosis, hemorrhage, and hemorrhagic erosions frequently result (62, 63).

Trauma: *Mechanical*. When the mucosa of the stomach is struck a sharp blow, blanching occurs for one to five seconds and is followed by transitory reddening for three to ten seconds (31, 49). Carlson (49) pre-

sumes that this reaction is due to a contraction of the muscularis mucosæ, which is known to contract when tapped. Suction of 40 mm. Hg applied for one minute causes hemorrhage which becomes black in 15 minutes (31). Spasm of the pyloric antrum caused by stimulating the vagi or by vomiting causes localized hemorrhage in the mucosa. This has been attributed solely to mechanical rupture of the capillaries; whether other factors such as a nervous disturbance of the circulation of the mucosa or the local release of acetylcholine or histamine, are also concerned is conjectural.

Chemical. The susceptibility of the gastric and intestinal mucosa to extrinsic chemical trauma has been discussed previously (see 261). Irritants, such as acid and mustard oil, cause first an active hyperemia with augmented secretion of mucus. This is followed by congestion, edema, petechial hemorrhages, and active bleeding. The irritated mucosa becomes much more susceptible to minor mechanical trauma (31).

Caloric. In an incomplete and unpublished study, Orndoff and I observed that hyperemia was caused by the perfusion of water at 42° C. through a Pavlov pouch in the dog. Edema and histologic evidence of cellular injury and a suppression of the secretion of acid were found when water at a temperature of 56° C. was perfused through the pouch for one hour. This is the temperature at which fibrinogen and some albumins are coagulated.

Recently we (72) have studied the question of thermal injury to the gastric mucosa. In a large group of subjects, the average temperature at which hot drinks could be swallowed rapidly was 57.8° C. The values ranged from 51° to 68° C. By means of intragastric thermocouples in human subjects, it was found that the highest temperature that occurred in the stomach was 50° C. when water at 68° C. was ingested and 55° C. when cornmeal at 85° C. was eaten. Although 20 to 30 minutes usually were required for the intragastric temperature to return completely to normal, the initial reduction in temperature was precipitous so that at the end of five minutes the temperature had descended half of the distance between the peak value and the normal level. Acute experiments on dogs showed that the minimum temperature at which injury to the gastric mucosa could be produced was 50° C. At this minimum temperature a minimum exposure of 10 seconds was required, whereas at higher temperatures a shorter exposure would suffice to produce injury—for example, at 65° C. only two seconds' exposure was required. From these observations it is evident that the ingestion of hot foods and drinks does not elevate intragastric temperature high enough and for a sufficient length of time to lead to acute thermal injury. The possibility of chronic damage from the repeated action of lesser grades of temperature still remains to be considered.

Comment

It would appear that the most significant point which arises from the going analysis is that a congested mucosa, regardless of cause, is more eptible to hemorrhage secondary to mechanical trauma. If the con- ion occurs in small areas and does not interfere with the formation of l by the parietal cells, the anoxic tissue in the congested area should be e subject to autodigestion.

What Normal Mechanisms May Be Perverted to Cause Vascular Disturbances?

Since vascular disturbances are so intimately concerned with the ology of erosions and acute ulcers, it is appropriate to inquire concern- what normal mechanisms may be perverted to cause vascular disturb- es. It is not difficult to conceive of how circulating bacteria, bacterial ns, or metabolic toxic agents might cause focal anemia and hemor- gic necrosis. But, so many patients with peptic ulcer appear not to bor focal infections or to produce metabolic toxins that the considera- of other possible causes of erosions and acute ulcers is necessary.

Nervous Factors: *Vasomotor Control.* It is well recognized that the nchnic nerves cause vasoconstriction of the blood vessels in the nchnic area. Stimulation of the splanchnic nerves causes a blanching he gastric mucosa in the dog, a fact easily demonstrated. The injection pinephrine also causes blanching of the mucosa in man (31) and the followed by secondary hyperemia. The vagi when stimulated electri- y for several minutes cause a hyperemia (67, 68). A vagal effect should se vasodilation, as has been observed in an "aggressive attitude" of iety, resentment, and frustration in man (31, 69).

Motor Control. The vagus nerves are predominately motor and the pathetics are predominately inhibitory to the gastric musculature. eir effect on the muscularis mucosae is unknown.

Secretory Control. The vagi stimulate and the splanchnics inhibit the retion of acid and pepsin. The splanchnics inhibit and the vagi stimu- the secretion of Brunner's glands (70).

Comment. The overaction of the splanchnics should cause blanching he mucosa, a decrease in the secretion of acid-pepsin, and a depression gastric motility. Such a reaction has been observed in the stomach of n in the presence of "fearsome shrinking and a desire to escape" (31). overaction of the vagi should cause hyperemia and increased motility secretion. Such a reaction has been observed in the stomach of man he presence of an "aggressive attitude" associated with anxiety, re- ment, and frustration (31, 69).

Thus, overaction of the vagi should predispose to erosions and ... ulcers of the stomach, which should not be true of overaction of ... splanchnics, unless the vasospastic factor is sufficient to cause a signific... amount of ischemia. In the case of the duodenal antrum, overaction ... the vagi should cause hypermotility, vasodilatation, and increased se... tion, and overaction of the splanchnics should cause hypomotility, v... constriction, and decreased secretion. The total picture of v... overaction would be hypermotility and vasodilatation of the stomach ... duodenum, an increase in secretion of acid by the stomach, and alka... fluid by the duodenum. The total picture of splanchnic overaction w... be hypomotility and vasoconstriction of the stomach and duodenum, ... a decrease in the secretion of acid by the stomach and an alkaline flu... the duodenum. The relation of the factors or the two total pictures ... the production of erosions of the duodenum is at present complic... and conjectural.

Local Humoral Factors: *Histamine*. Babkin (71) has suggested ... since histamine is presumably liberated during normal secretory proc... in the stomach, it may be formed in excess in an area and cause a l... vascular disturbance, such as capillary stasis and hemorrhage. At ... same time, its excess formation may act on the parietal cell to cause ... increased secretion of acid. He suggests that a local vascular disturb... may be the cause of an excessive release of histamine. Dragstedt (61) ... suggested that trauma to the mucosa may be the cause of the exce... release. A local gastritis may also be responsible.

Acetylcholine. Necheles and his associates (96) have suggested ... continuous or an excessive production of acetylcholine, which is pro... by vagal or cholinergic nerve endings, may cause vasoconstriction, fol... by an erosion. Acetylcholine may in small doses on isolated or exposed ... organs cause vasoconstriction, but this is contrary to the effect of ... effective doses of the drug on vessels in situ where it causes vasodila... It is contrary to the effect of stimulation of the vagus which ... vasodilatation. And, in our hands, large doses cause vasodilatation ... bleeding from the pyloric mucosa due to the effect of vigorous co... tions in the presence of a congested mucosa. If the postganglionic ... acetylcholine by vagal nerve endings is a cause of erosions, it ... appears to cause them by producing exaggerations of the motor ... hypermotility (38).

Cause of the Focal Nature of the Lesions

The cause of the focal nature of the lesions has not been ... would be very difficult to demonstrate. In cases where only a single ... causing injury is used. For example, when the mucosa is protected ...

dilute acid solution, though the tips of all the villi show evidences of jury, only one or two areas actually ulcerate unless the concentration of id is excessive. Several explanations have been offered for the phenomon since it occurs in many tissues other than the stomach and intestine:

1. All of the arterioles are not equally patent at the same time. This ould cause unequal distribution of a toxic agent.

2. The cells in all areas may not be similarly active and hence variaons in susceptibility may occur.

3. The muscularis mucosae and propria, by being in various states of ntraction, may mechanically affect the distribution of the blood or cause equally distributed trauma.

4. The vasomotor nerve endings may be in various states of activity d respond differently to the insult.

5. In response to a disturbance in an area, a reactive hyperemia and a mulated increase in resistance by local humoral mechanisms may augent the defense of surrounding tissues.

The Type of Acute Lesion Which Develops into a Chronic Ulcer

In Animal Experimentation

There are only two types of typically chronic ulcer which are known to ise quite regularly from an acute lesion of known type. One of these is e postoperative jejunal ulcer which occurs spontaneously in the jejunum the dog after gastrojejunostomy and diversion of the bile and pancreatic ice into the lower ileum (the Mann-Williamson dog: the M-W dog). he other occurs spontaneously in the stomach of the rabbit after bilateral gotomy when the animal is fed the usual rough diet. A defect in the stric mucosa of the rabbit produced by excision frequently produces an cer that is typically chronic, but may heal in time without therapy.

Postoperative Jejunal Ulcer in the Dog. The development of this cer has been studied satisfactorily. The earliest stage reported by Mann d Bollman [23] appeared as a "saucer-like depression" in the jejunal ucosa "covered with a homogeneous gray membrane." "When the embrane at the site of the beginning ulcer was gently sponged off, a ght depression was uncovered where the surface of the mucosa had dispeared and which bled profusely." Microscopically at this stage, "the jury involves only the tops of the tubules," the hemorrhage occurring tween the tubules. "The lesion quickly penetrates below the muscularis ucosae." In the course of therapeutic studies on the healing of jejunal cer in the M-W dog, we [28, 37] have observed the type of lesion deibed by Mann and Bollman (Fig. 45). A later type of lesion is shown in



FIG. 45. Ulcerative lesion of the jejunum as visualized at exploratory operation in a Mann-Williamson dog. This lesion was found to be completely healed after 15 days on therapy. (Orndorff et al.: *Am. J. Digest. Dis.*, 3: 26, 1936.)

figures 36 and 37. In figure 36 the lesion is punched out, and has hemorrhagic margins and a gray base. The very earliest lesion we have seen consisted of a hyperemic, but not cyanotic, area approximately 10 mm. in diameter, which bled when rubbed gently with the finger and profusely when rubbed with moist gauze. This lesion may have been covered with a gray membrane prior to opening the jejunum. It is known from exploratory laparotomy followed by later surgery or autopsy that these early lesions extend and become chronic or perforate (37).

The earliest lesions which have been seen in the stomach of the vagotomized rabbit are of the nature of hemorrhagic erosions. Aside from the Mann-Williamson operation and the experiments on the rabbit, however, several instances are known in which a single experimental procedure has first produce hemorrhagic or anemic erosions and later chronic or perforating ulcers. But, whether the acute lesion, which gives rise to a chronic or a perforating ulcer, is initially a hemorrhagic or anemic erosion, or an acute ulcer, is undetermined.

PHARMACOLOGIC AGENTS. A few examples will suffice to illustrate the point. In the case of cinchophen-induced ulcers, this transformation from the acute diffuse to the chronic single ulceration has been carefully stu-

e p. 183). Similarly, histamine, in acute and semi-acute experiments, oduces the characteristic diffuse type of ulcerative gastritis (see p. 214), ereas, when allowed to act continuously by implantation in beeswax e p. 213), chronic ulcers of the stomach and duodenum result. Caffeine nother example of an agent which produces hemorrhagic erosions of fundus when acting over a short period but results in chronic ulcers in region of the prepyloric area, or lesser curvature, or duodenum, when ministered over an extended period in beeswax.

Thus, cogent evidence exists which points to an essential relationship ween the acute and chronic types of ulcerative process. It would appear t the fundic mucosa is more susceptible to the immediate effects of the erogenic agent, manifesting a diffuse ulcerative gastritis which, how-r, has a marked tendency to heal even though the ulcerogenic agent tinues to be exhibited. The pyloroduodenal mucosa, as well as the nal mucosa, on the other hand, displays some resistance to the early cts of ulcerogenic agents but shows a marked tendency toward chro-ity of the lesions which ultimately occur. Nevertheless, in the considera-n of experimental results, it remains essential to demonstrate that each en ulcerogenic agent is capable of producing typical chronic ulcer ore its significance can be established because it is probable that agents st (particularly those causing widespread damage in organs other than stomach and duodenum) which produce only acute changes which uld not eventually transform into the chronic or acute perforating type. s also important to determine the nature of the initial lesion which gives to the ulcer.

In Man

Aschoff (29) assumes that chronic or perforating ulcer may develop m a simple erosion when it occurs in the region of the lesser curvature or orus. Hauser (4) believes that it is improbable that such ulcers develop m erosions and suggests that they arise from hemorrhagic infarcts of ious etiology which initially extend to or involve the submucosa. It has n indicated before (see p. 175) that pathologists and surgeons fre-ntly find erosions and acute ulcers associated with chronic or per-ating ulcers of the stomach or duodenum. That these acute lesions are an agonal phenomenon in ulcer patients has been demonstrated by the troscopic observations of Schindler and Baxmeier (19). They per-med 317 gastroscopic observations on 31 patients with benign gastric er. Hemorrhagic erosions or mucosal hemorrhages were found in 40 44 per cent of these cases as compared to an incidence of 5.6 per cent in 00 cases without peptic ulcer. These lesions occurred in the same areas the stomach in which the ulcer was present and usually occurs. The

gastroscopist has not, however, observed an erosion develop into an ulcer, according to our search of the literature.

Summary

The only experimental and morphologic evidence available indicates that the chronic ulcer of the stomach or duodenum originates from an acute ulcer of a nonspecific type.

A multiplicity of factors may operate to impair the mucosa by decreasing the protective mechanism or by increasing the action of aggressive factors on the mucosa so that an erosion and or an acute ulcer develops. These factors are outlined in Tables 4 and 5.

The anatomic types of initial lesions which have been described are: (1) Primary necrosis without and with subsequent hemorrhage, (2) primary interstitial hemorrhage followed by necrosis, and (3) inflammation of lymph follicles or "follicular ulcers." A single substance, or a combination of two substances acting together, such as caffeine and histamine, may produce both primary necrosis and primary hemorrhage concurrently.

An erosion and acute ulcer which has been studied from its inception is the caffeine-histamine gastric erosion and ulcer in the cat; the initial abnormality which causes this lesion is vascular in nature, though acid pepsin digests the ischemic tissue. The ulcer caused by cinchophen, on the contrary, is associated with a necrosis which does not appear to be primarily vascular in origin but appears to be due to an inflammation due to a toxic action on the epithelial cells.

Follicular ulcers have been described in infectious conditions, but all are agreed that the ordinary peptic ulcer is not a follicular ulcer. Congested mucosa regardless of cause is more susceptible to mechanical and chemical trauma. Anoxic tissue in a congested or ischemic area should be more subject to digestion.

The normal mechanisms which may cause vascular disturbances when perverted are: (1) Vasomotor nerves to the gastric mucosa, (2) nerves which cause contractions of the muscularis mucosae or muscularis propria and cause local hemorrhage, and (3) nerves which affect the secretion of acid-pepsin or of Brunner's glands. It has been suggested that the local release of excessive amounts of histamine or acetylcholine may be involved. There are numerous ways to explain the focal nature of the erosion or acute ulcer.

There are two types of typically chronic ulcer which are known to arise spontaneously and quite regularly from an acute lesion; one is the postoperative jejunal ulcer in the dog, and the other is the lesser curvature gastric ulcer which occurs in the vagotomized rabbit fed a rough diet. The same is true of certain pharmacologic agents. In man, though the

proof is not so good as in the dog, cat, and rabbit, there is no good reason to doubt that a "chronic" peptic ulcer arises from an acute lesion.

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OUTLINE OF CHAPTER 9

Role of Gastric and Duodenal Secretions

I. Role of the Gastric Juice
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CHAPTER 9

Role of Gastric and Duodenal Secretions

Role of the Gastric Juice

Sham Feeding

Apparently the first attempt to produce a physiologic hypersecretion in animals was made in 1899 by Panow (1), who sham-fed eight esophagostomized dogs and reported the development of perforating ulcers, one gastric and three duodenal, in four of the animals. No further details of this work are given in the German abstract of Panow's Russian thesis. In 1927, Silbermann (2) sham-fed 18 dogs three times daily for from 14 to 49 days.

> In every case without exception gastric or duodenal ulcers in various states of development . . . could be observed . . . By the end of the third week there were without exception well marked, mostly deep and indeed subserous ulcers.

As to the microscopic appearance of these lesions, Silbermann wrote:

> Histologic changes were present to the highest degree, according to the character of the ulcer . . . In the deeper ulcers, necrotic coagulation areas are found in the muscle layers down to the subserosa.

To illustrate this ulcer material, Silbermann published four figures. His Figure 1, a gross specimen, captioned "two large round subserous ulcers after a 47-day-long sham-feeding," is too poor a photograph to permit the reader to conclude anything about the alleged lesions; moreover, the specimen was prepared and mounted in such a manner as to render the anatomy of the stomach and duodenum unrecognizable. His Figure 2, "diffuse gastric ulceration of the cardial portion along the folds," shows numerous hemorrhagic erosions or erosive hemorrhages, and they seem rather to be among the rugae than along the longitudinal fold. His Figure 3 is a photomicrograph of an "ulcerative gastric defect reaching down to the submucosa"; and his Figure 4, "marked necrosis of a large section of the glands of Lieberkühn," shows an area of sloughing of the tips of the villi with the rest of the mucosa intact. It is unfortunate that Silbermann did not exhibit a single acceptable gross or microscopic picture of one of the numerous "well marked, mostly deep, and subserous ulcers."

The Silbermann experiment was repeated in 1929 by Brenckmann and White (3) and, in 1932, by Puhl and Broderson (4); these observers did not obtain any ulcers, but they considered that they had produced a gastroduodenitis, which they regarded as constituting the "pre-ulcerous terrain." Significantly, Puhl (5) stated that the same type of change could be produced by starvation. Büchner and Schneider (6) stated that they repeated Silbermann's work because his published figures did not bear out his conclusions. They claim to have obtained erosions in the stomach in three cases and a deep acute ulcer of the duodenum in a fourth after 7 to 14 days of sham-feeding in seven dogs. This was interpreted as providing further support for Büchner's theory that peptic ulcer is caused by hypersecretion. It is odd that these authors, having commented on the inadequacy of Silbermann's illustrations, published no data or pictures of their own—unless they appeared in some subsequent paper which we have been unable to find.

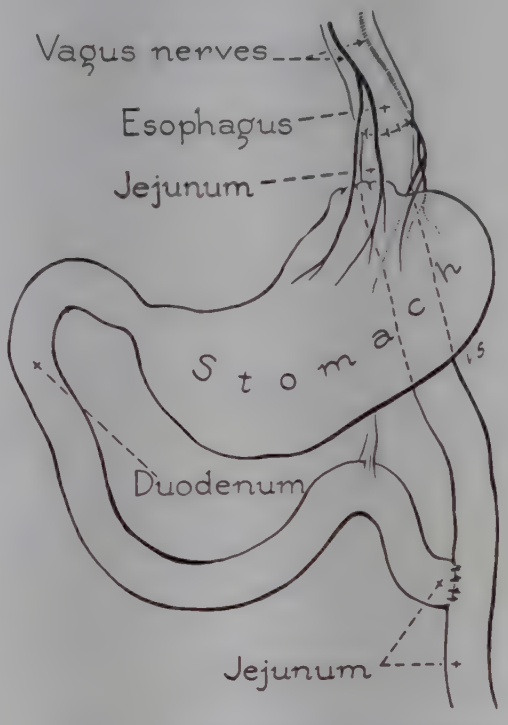


FIG. 46. Preparation providing for secretion of gastric juice into the empty stomach by both nervous and humoral stimulation. (Redrawn from Matthews and Dragstedt: *Surg., Gynec. & Obst.*, **55:** 265, 1932.)

Matthews and Dragstedt (7) sham-fed three dogs daily for one month, at the end of which time no ulcers were found. In a further experiment, they prepared a dog in such a manner as to provide for the secretion of gastric juice in the empty stomach by both nervous and humoral stimulation (Fig. 46); no lesion developed in the stomach, duodenum, or jejunum in an observation period of 70 days. No data on the level of acidity attained were submitted for any of the experiments.

Such was the unsatisfactory status of the problem when Fogelson undertook a thorough reinvestigation of the effects of sham-feeding on the upper digestive tract. Schmidt and Fogelson (8) sham-fed 10 dogs three times daily. Analysis of the gastric juice secreted in response to the sham-feeding yielded acidity values as high as, or higher than, those reported by Silbermann. Five dogs, kept on a submaintenance diet in order to permit a loss of weight, were sham-fed from 20 to 60 days; no erosions, ulcers, or scars were observed. The remaining five dogs were sham-fed for 72 to 102 days; in addition, to augment the acid irritation of the duodenum, 300 cc. of 0.36 per cent HCl was introduced into the stomach twice daily

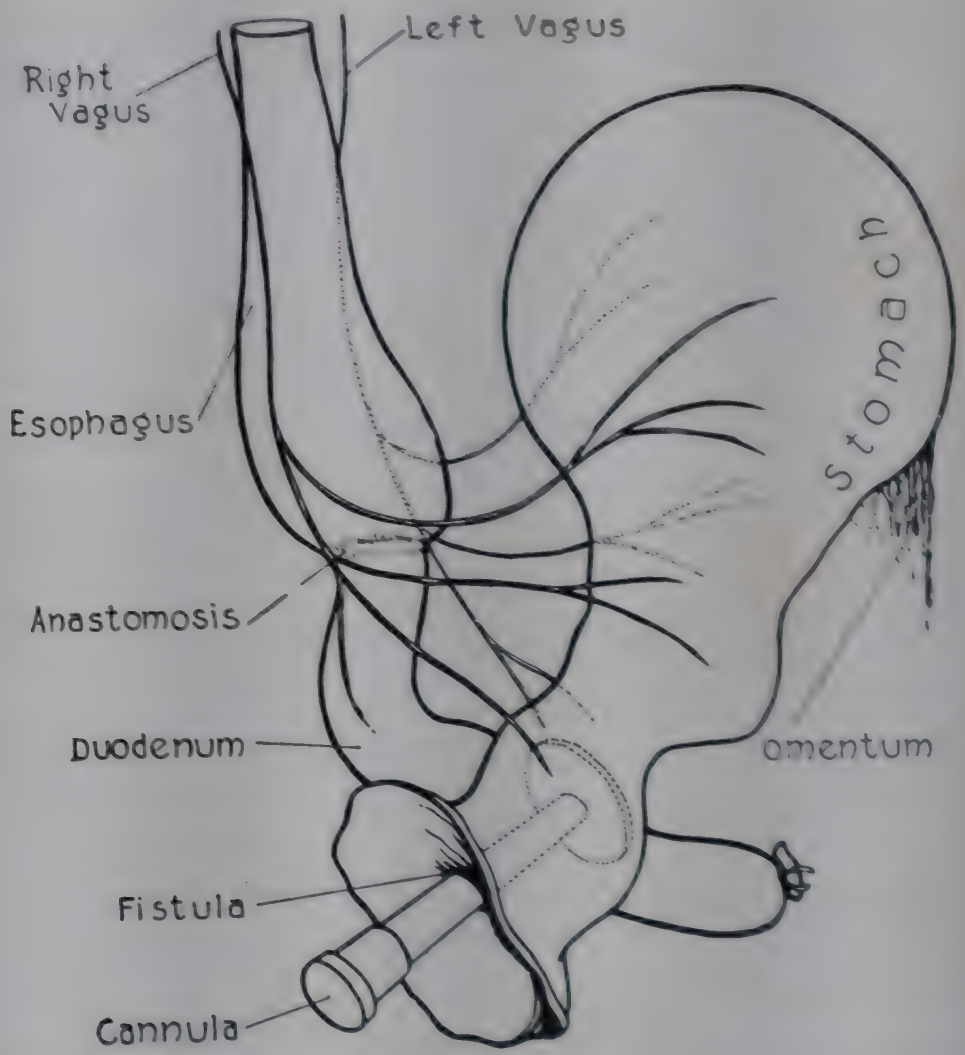


FIG. 47. Vagally innervated pouch of the entire stomach. (Courtesy, Dragstedt and Ellis: *Am. J. Physiol.*, **93:** 407, 1930.)

after the fiftieth day. When the dogs were sacrificed, the only finding was hemorrhagic duodenitis; there were no ulcers or even erosions.

COMMENT. When experiments such as those carried out by Schmi and Fogelson do not result in ulcers, one is forced to look with circum spection on any report which claims positive results by this method with the same period of time. It is conceivable that, if these experiments we prolonged indefinitely, duodenal ulcers might ultimately result. Howeve the sham-feeding technic, as carried out by these investigators, does n simulate adequately the continuous secretion, particularly the nig secretion, of duodenal ulcer patients. An esophagostomized dog w sham-feed voraciously for from 30 to 45 minutes at a time before desisti the stimulation of secretion then continues for perhaps an hour. T stomach and duodenum are thus subjected to the action of acid unbuffe by food for a period of from one to two hours thrice daily. Of course considerable reduction of this acidity is brought about by the alka

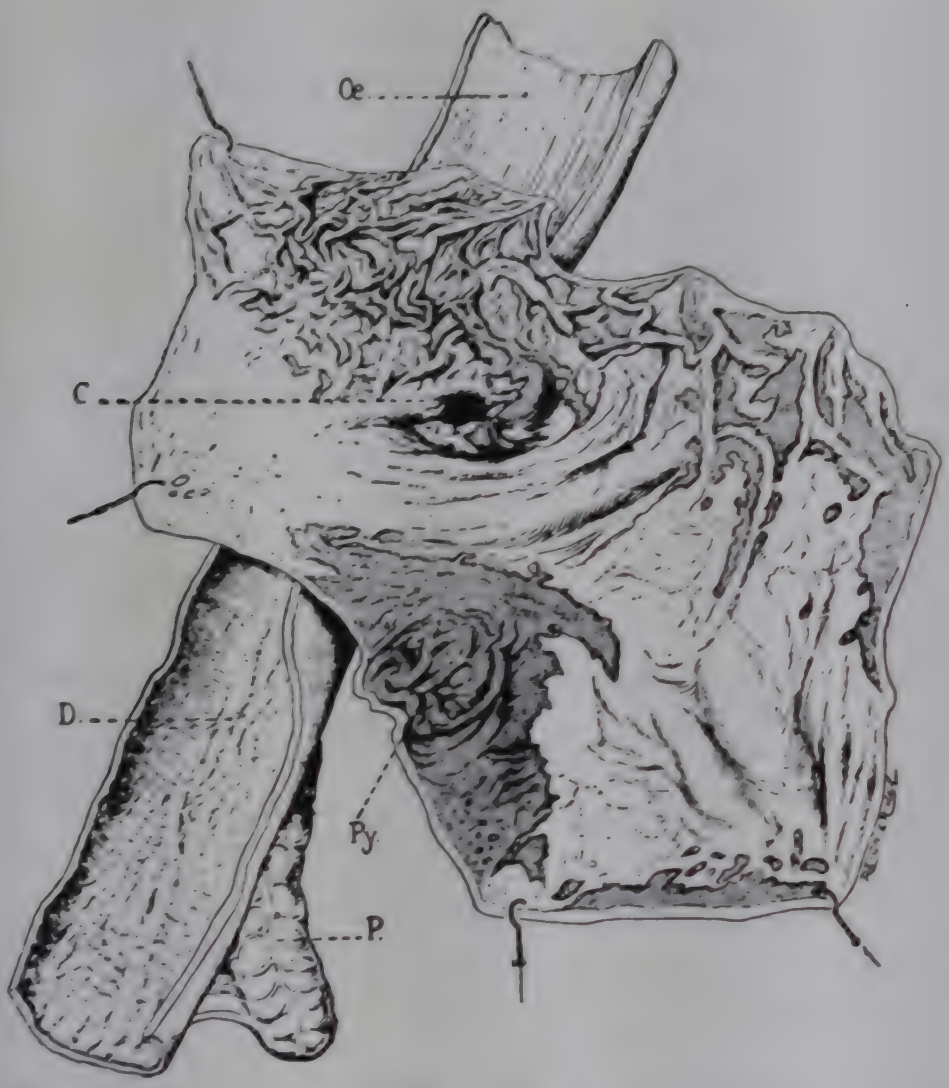


FIG. 48. Ulceration in the stomach which has been converted to a pouch and secretions retained. *C*, cardia; *D*, duodenum; *Oe*, esophagus; *P*, pancreas; , pylorus. The surviving mucosa is represented in gray. (Courtesy, Frouin: *esse méd.*, 1908, p. 769.)

uodenal juices, and it is this factor which probably protects these dogs om ulceration. For example, Dragstedt (9) observed ulceration in gally innervated pouches of the entire stomach (Fig. 47), and he and hers have shown that ulcers develop in a segment of intestine anastoosed to a pouch of the fundus of the stomach (see p. 311); but when the gally innervated stomach and upper intestine were isolated in such a ay that food could not enter, neither the stomach nor the duodenum owed any ulceration up to 70 days. The latter experiment was performed only one dog, and should be repeated in a large series of animals.

There is no doubt that the resistance of the gastric mucosa to digestion naturally secreted gastric juice can be overcome. But in all cases where is has been accomplished, factors have been introduced which do not cur, or have not yet been shown to exist, in peptic ulcer patients.

Frouin (55, 56) found that if the strongly acid secretions are retained in the stomach by obstructing its outlets, ulceration results (Fig. 48). He concluded that the evacuation of gastric juice from the stomach protects the organ against the noxious action of its secretions. Since then, numerous investigators (9, 57, 58, 59, 180) have reported the occurrence of ulcer in gastric pouches when the secretions are prevented from draining away. In these circumstances it is possible that the intragastric pressure is sufficient to interfere with venous return or with oxygenation of the cells. However, when this is controlled ulcers still occasionally occur.

Histamine

Büchner and his associates (10, 11) observed erosions and acute ulcers in the stomachs of rats receiving subcutaneous injections of histamine after a 24-hour fasting period; the significance of these findings was rendered questionable by the appearance of similar lesions in fasted controls. However, Bürkle-de la Camp (12) denied that fasting alone caused ulceration in rats; according to his observations, administration of histamine combined with alternate feeding and fasting was followed by a high incidence of gastric ulcers.

In cats, McIlroy (13) found that the injection of histamine on alternate days delayed the healing of acute gastric ulcers produced by excision. O'Shaughnessy (14) obtained ulcers in two cats by direct injection of histamine into the wall of the stomach, but could not produce any lesions by subcutaneous injections of the drug. Heinlein and Kastrup (15) administered histamine intravenously to cats in graded daily doses for as long as 30 days. The final dosage varied from 1.5 to 8 mg. A gastritis characterized by punctate hemorrhages, generally on the crests of the mucosal folds in the antrum, was observed in all these animals. There were no ulcers.

Merkel (16) studied the effects of histamine in 11 guinea pigs over a period of 11 hours, during which the animals received injections of 0.13 to 0.28 mg. per 100 Gm. of body weight every half-hour or hour. Erosions developed in all cases, leading to perforation in four animals. In a further series of 44 guinea pigs, the author administered daily injections of 0.18 to 0.45 mg. per 100 Gm. up to 189 days, with an average of 80 days. Lesions of the stomach were observed in 93 per cent of the cases; in an occasional animal there developed an ulcer similar in gross appearance to the chronic human ulcer except that the lesions in the guinea pigs were never on the lesser curvature and were almost exclusively in the corpus and fundus. A similar distribution was observed by Crane et al. (17).

In dogs, the subcutaneous or intravenous injection of histamine in varying dosage once daily or oftener for a varying period of time has been

reported to cause erosions or ulcers, or both, by several investigators (18, 19, 20, 21). Overgaard (22) reported negative results in five dogs receiving 0.5 mg. of histamine subcutaneously daily for eight months. We (23) gave 2 mg. of histamine subcutaneously every two hours, day and night, for two months to 11 dogs; in no instance did we observe any ulcers in these animals.

A method for producing gastric and duodenal ulcers regularly with histamine was discovered in 1940 by Code and Varco (24), who noted that the injection of a suspension of histamine in beeswax caused a sustained secretion of highly acid gastric juice in dogs. These investigators and their associates demonstrated that the daily intramuscular implantation of histamine in beeswax in doses varying with the size of the animal resulted in the development of peptic ulcer in the dog (25), cat (26), guinea pig, chicken, duck, pig, woodchuck, calf, monkey, and rabbit (27). In all except the monkey and rabbit, the ulcers were produced in 50 per cent or more of the animals. Rabbits were found to be particularly resistant to the development of histamine ulcers, but were later shown to be as susceptible as other species when placed upon a liquid diet (185).

The production of ulcers in dogs by the method of Code and Varco has been confirmed (28, 29).

Mechanism of the Histamine Ulcer. Opinion is divided regarding the pathogenesis of the acute gastric lesions which results from the action of histamine. Code (30) represents the school of thought which holds that the effect of histamine is due primarily to the corrosive action of the continuously secreted gastric juice. The volume and acidity of this juice are certainly impressive. For example, after the intramuscular injection of 30 mg. of histamine in beeswax (divided between two injection sites), Code and Varco (33) collected from a Heidenhain pouch 675 cc. of juice in 24 hours, having an acidity of just under 150 m Eq./1. In the same dog, the 24-hour volume following a control injection of beeswax without histamine amounted to 15 cc.

In view of the large volume of highly acid juice secreted under the influence of histamine-in-beeswax in the dosage used, there is a possibility that the gastroduodenal ulceration which results is due to an exhaustion of the neutralizing capacity of the duodenal secretions. Certainly the gastric acidity as recorded by Code and Varco exceeds that observed by Berk et al. (34) in studies in which they reported inadequate duodenal neutralization in some instances following single injections of aqueous solutions of histamine. More pertinent, it would seem, are the observations of Stevens (179), who estimated the capacity of the duodenum to buffer and neutralize acid introduced through a fistula and recovered by means of another fistula at a lower level (Fig. 49); from the data obtained, the author calcu-

lated that the duodenum was capable of neutralizing an average of 1800 cc. of 0.5 per cent HCl in 24 hours, an amount considerably in excess of physiologic needs and probably in excess of that secreted by dogs receiving histamine in beeswax. Other considerations which enter into the question of whether the ulcers following administration of histamine in beeswax are due primarily to acid will be discussed later.

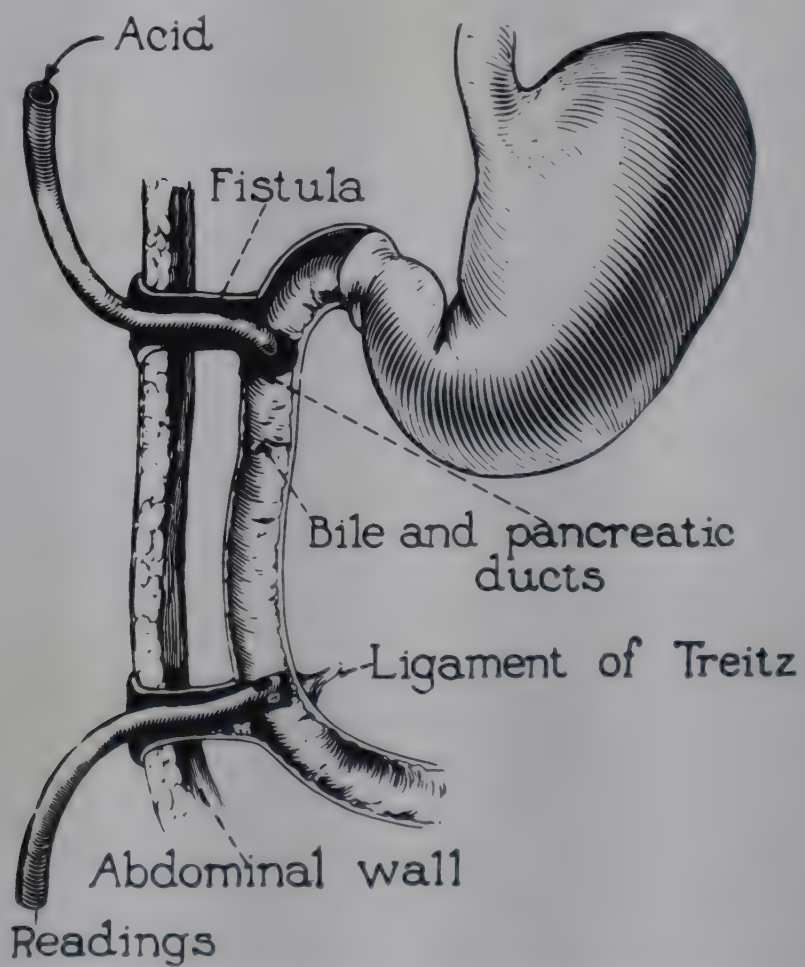


FIG. 49. Preparation for the study of the neutralizing, buffering, and diluting capacity of the duodenum. (Courtesy, Stevens: *Am. J. Digest. Dis. & Nutrition*, **2**: 288, 1935–36.)

Recent German observers (15, 16) contend that the vasodynamic and angiotoxic effects of histamine are the basic factors, in that they impair the vitality of the mucous membrane sufficiently to render it susceptible to gastric juice of ordinary volume and acid-pepsin concentration. This view is based on histologic studies of the stomach after administration of histamine, without, however, satisfactory proof that the observed changes would occur in the absence of acid.

For instance, Merkel (16) describes the sequence of events in guinea pigs as starting with a patchy or diffuse hyperemia; this progresses to

stasis, and finally to thrombosis and hematin formation. The latter is attributed by Merkel to the fact that the increased capillary permeability caused by the histamiue permits acid to diffuse into the capillaries. As evidence of the absence of corrosive action of acid in the first stages of the necrotic process, he cites the observation that the detached epithelium retains its normal structure. Thus Merkel concludes that the ulcerogenic action of histamine is based primarily on circulatory impairment. In our opinion, his observations do not adequately exclude acid as a primary factor because, as will be shown in the following pages, all of the above changes have been produced (31) by the direct application of 0.1 N HCl to the stomach and intestine. However, the histopathologic process in the histamine experiments described by Eppinger and Leuchtenberger (32) in dogs and by Heinlein and Kastrup (15) in cats, begins with *edema*, which is strong presumptive evidence for the belief that "in histamine gastritis the initiating factor is not the acid, but a direct toxic action, especially a vascular effect, as occurs in other organs" (15). Merkel (16) also described edema, principally of the mucosa but also involving the deeper layers; however, he interpreted this as a late development. On the contrary, Heinlein and Kastrup (15) leave no doubt that in their

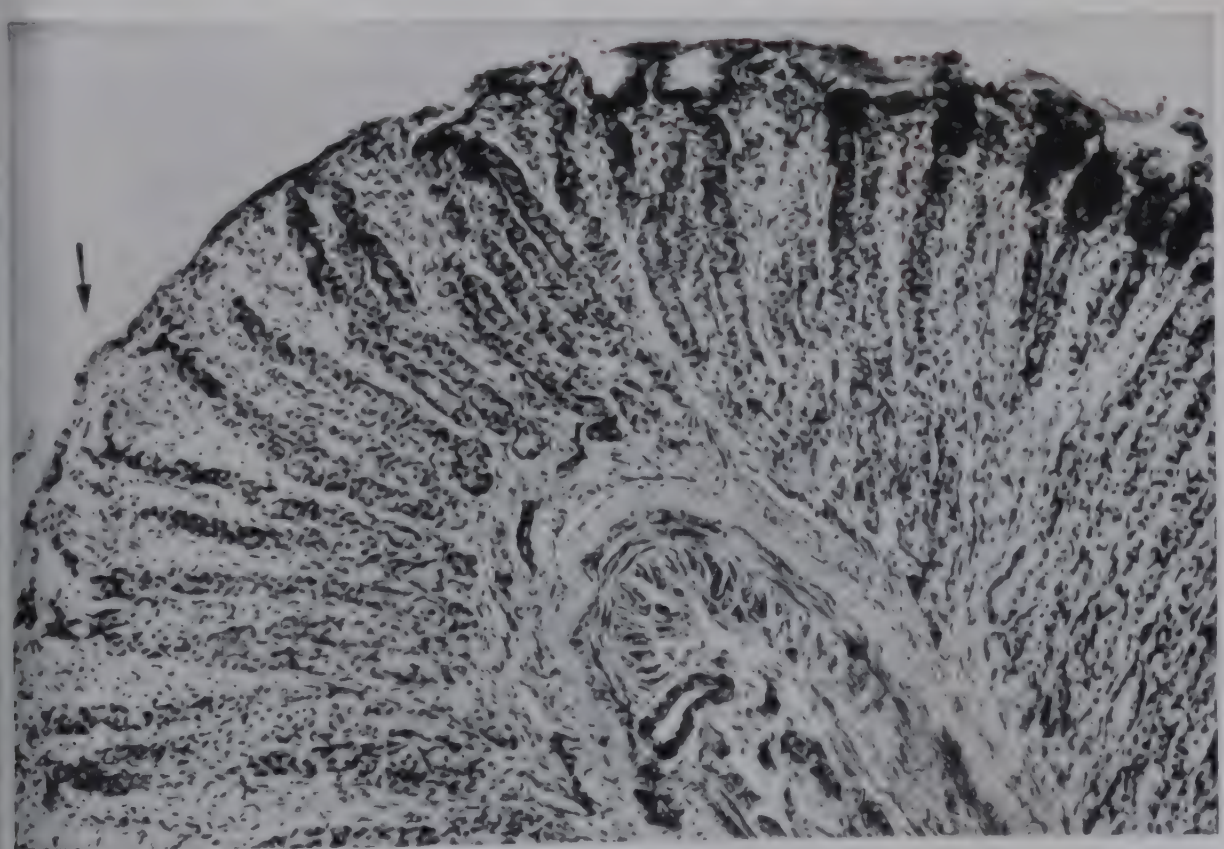


FIG. 50. Gastric mucosa of the cat after parenteral administration of histamine. Arrow indicates point of greatest subepithelial edema. (Courtesy, Heinlein and Kastrup: *Ztschr. f. d. ges. exper. Med.*, **102**: 517, 1938.)

experiments the earliest and most striking change was an intense subepithelial edema (Fig. 50) such that the epithelial layer was in some areas completely separated from the underlying tissue. They state:

> The surface epithelium was entirely absent in places, without there being, as a rule, any fibrinoid necrosis present. Where fibrinoid necrosis was present, it was rather superficial, and gave the impression of secondary digestion of the swollen epithelium.

The fact that similar, though less marked, changes were demonstrable in the intestine strengthened the authors' conviction that acid was not the initiating factor in the histamine ulcer.

One of the difficulties involved in the interpretation and correlation of these observations is the species difference in the reactivity of animals to histamine.

Experiments performed in an effort to prevent the histamine ulcer have not aided materially in clarifying the mechanism. Shoch and Fogelson (28) were able to delay or prevent the development of ulcers in four dogs receiving histamine in beeswax by administering 0.5 Gm. of a pepsin-inactivating substance (sodium lauryl sulfate) twice daily. This would indicate that the acid-pepsin, but particularly the pepsin, is the predominating factor in the etiology of these ulcers. This is interesting because there is a disagreement as to whether histamine stimulates any pepsin secretion; Babkin (35) maintains that it does not, while we (36) interpret our observations as proving that it does. The prevention of histamine ulcers by a pepsin inactivator would not, however, be conclusive evidence against Babkin's position, because these dogs are fed, usually, once daily, and it might be argued that it is the pepsin formed in response to the meal which does the damage. At any rate, the experiments of Shoch and Fogelson are of sufficient importance to justify further inquiry. Since all dogs do not develop ulcer when given histamine in beeswax, the failure of their four dogs to develop ulcer may have been due to random sampling or chance.

That a motility disturbance is not concerned in the ulcerogenic action of histamine is indicated by reports that atropine (16) and vagotomy (37) do not prevent histamine ulcers.

Crane et al. (17) reported that the injection of benadryl in doses sufficient to prevent anaphylactic shock did not affect the development of histamine-induced ulcers in guinea pigs. The authors did not report any determinations of gastric secretion. However, we (38) could demonstrate no inhibition of histamine-stimulated gastric secretion in total pouch dogs receiving benadryl. These observations are of potentially great significance. If it can be shown that benadryl, or any potent antihistamine drug, prevents the angiotoxic effects of histamine without inhibiting the formation of histamine ulcers, it would speak against the angiotoxic mechanism in the

pathogenesis of these ulcers. The failure of antihistaminic drugs to prevent histamine-induced ulcer has been confirmed by several groups of workers (46, 111, 131).

In the case of the Mann-Williamson dog, in which the jejunal ulcers have been shown to be due to the unopposed action of acid gastric juice on a susceptible mucosa, we postulated that the hypersecretion was partly a result of abnormal histamine formation in the irritated intestine. Since enterogastrone has a high protective value against M-W ulcers, we (29) tested its effect on the histamine-induced ulcer. It had none.

Comment. Although the acid versus vascular theories of histamine-induced ulcer have been debated, particularly in the German literature, for a number of years, it was not until the work of Code and Varco that ulcers could really be produced, at least with any regularity, by the use of histamine. For example, we (23) administered 2 mg. of histamine to dogs every two hours for up to 66 days, in an effort to achieve a continuous secretion of acid, but we did not produce any ulcers; it therefore came as a surprise to us to learn that the histamine in beeswax method resulted regularly in the development of peptic ulcers in most laboratory animals. Indeed, the development of gastric (39, 40) and duodenal (41, 48) ulcer in humans through the action of histamine has been described. Reports that the blood histamine is (42) or is not (43) elevated in hypersecreting patients are of doubtful significance because the response of the parietal cell is in itself probably the most delicate of all tests of histamine action; i.e., a concentration of histamine in the blood sufficient to cause a definite increase in gastric secretion may be too small to be detected by any test now in use.

The foregoing discussion indicates that it cannot be unequivocally assumed that the histamine ulcer is due to the corrosive action of gastric juice alone. We have noted (44), for example, that if the maximum acid-stimulating dose of histamine is exceeded, the development of ulcers is accelerated. This might be interpreted as indicating that the acidity alone cannot be the answer, because if it were, then additional histamine should not intensify the ulcerogenic action. On the other hand, it may be that the maximal acid-stimulating dose is below the maximal angiotoxic dose.

Instillation of Acid or Acid-Pepsin into the Stomach

Acid. Puhl (5) introduced 0.4 to 0.6 per cent HCl into the stomach of dogs and produced degenerative and erosive changes in the stomach and duodenum; details of the frequency and duration of the instillations were not given. Schmidt and Fogelson (8) introduced 300 cc. of 0.36 per cent HCl twice daily via esophageal fistula into the stomach of dogs which had been sham-fed for 50 days. After 10 days, the concentration of the instilled

acid was increased to 0.5 per cent and continued up to 42 days. None of these dogs developed erosions or ulcers. Overgaard (22) gave 350 to 400 cc. of 0.5 per cent HCl once or twice daily to dogs for periods of from 5 weeks to 4½ months; antral gastritis was produced, but no ulceration. Gage et al. (21) fed eight dogs 1 per cent HCl in unstated amounts three times every other day for as long as 55 days without producing chronic ulcer.

Subacute or chronic gastric ulcers were reported in dogs by Mann and Bollman (45) after about four weeks of instilling 0.4 per cent HCl into the stomach via gastric fistula. The acid was introduced for eight hours daily at a rate of less than 1 cc. per minute. These results could not be duplicated by Wangensteen et al. (46), who were unable to produce ulcers in four dogs by perfusing 82 to 108 cc. per hour of 0.4 per cent HCl 6½ to 7 hours daily for 15 to 46 days. In cats, however, 40 to 50 per cent as much acid (which, on the basis of body weight, represents two to three times as much) over the same period resulted in ulceration of the esophagus, cardiac stomach, fundus, antrum, and duodenum in three of four animals in 4 to 11 days. Gotschlich (47) reported minute focal erosions in fasting cats after the introduction of 15 to 20 cc. of 0.8 to 1.5 per cent HCl by stomach tube. Schiffrin and Warren (49) produced an ulcer in one of three cats by introducing 30 cc. of 0.1 N HCl into a gastric fistula hourly for eight hours daily. Howes et al. (50) reported that the healing of excision ulcers of the stomach in cats was not affected by perfusion with HCl of pH 1.1, but was delayed by acid of pH 0.9. Even with the latter concentration, however, chronicity could not be induced.

According to Matzner and his associates (51, 52), the substitution of 0.3 per cent HCl for drinking water caused only an occasional ulcer of the prostomach in rats.

In view of the disagreement in the literature regarding the production of peptic ulcer by intragastric instillation of acid, we (53, 186) recently reinvestigated this problem, principally because we believed that the experiments performed in the past were poorly designed. They were poorly designed in that the acid was introduced in such a manner as to cause an intense acidosis, a condition which does not occur in association with endogenous hypersecretion.

When 0.10 N HCl was instilled continuously for two to four days into the stomach of dogs via gastrostomy at a rate of 8 to 10 cc. per kilogram body weight per hour, all of the animals developed duodenal ulcers, sometimes accompanied by pyloric ulcers. The blood pH of these dogs fell as low as 6.9, so, in a second series of animals receiving the same amount of acid intragastrically, sodium bicarbonate solution was given continuously intravenously, or by ileostomy at a rate sufficient to maintain the blood pH

at a normal value. None of these animals developed ulcer even though the experiment was continued for as long as 10 days. The addition of 0.2 per cent pepsin to the 0.10 N HCl solution did not cause ulcers to appear, but, when the concentration of acid in the acid-pepsin solution was raised from 0.10 to 0.15 N, ulcers occurred in all seven of the dogs which lived for six or more days in spite of the maintenance of normal acid-base balance.

From these studies we have concluded that under our experimental conditions the threshold of acid concentration which is capable of producing ulcer in the dog is between 0.10 and 0.15 N. Whether a lower volume rate of infusion would lead to ulceration remains to be determined. It is of interest to compare the rates of acid administration which we used in these experiments with the maximal secretory capacity of the dog's stomach. We (187) have found that the maximal secretory rate which can be evoked by histamine is about 8 cc. per kilogram body weight per hour and this secretion contains HCl in a concentration of 0.14 N, on the average. In dogs with vagally innervated pouches of the entire stomach, Dragstedt and Ellis (54) observed maximal secretory rates of 2600 cc. per day containing HCl in a concentration as high as 0.14 N. In other words, in the series of experiments, in which ulcer occurred with normal acid-base balance, we infused acid into the dog's stomach at a concentration and rate slightly greater than the average maximal secretory capacity when stimulated with histamine.

Comment. The acid-base balance of the animal in relation to ulcer formation has received little attention. Mann and Bollman (45), who used the CO_2 combining power of the blood as an index of acidosis, state that "the amount of acid . . . administered does not appear to be sufficient to influence greatly the acid-base equilibrium of the blood." They did not administer as much acid as we did.

In the hypersecreting patient there should theoretically be no acidosis, since the acid is reabsorbed. Nevertheless there is the possibility that some of the base lost in the urine during the "alkaline tide" might not be replenished adequately in the ulcer patient. As far as we are aware, the acid-base balance in peptic ulcer has not been shown to be disturbed. Balint (181) believed he had evidence that the blood and tissues in ulcer patients were more acid than in normals, but his work could not be confirmed (182, 183).

These experiments demonstrate that, in order for excessive acid secretion *alone* to provoke duodenal ulcer, the gastric glands must secrete at their maximal capacity day and night for from five to ten days.

The results of these experiments suggest that the continuous presence of histamine in the circulation may cause ulcer solely by an increase in the

secretion of gastric juice above the tolerance of the duodenal or pyloric mucosa.

However, they clearly demonstrate that the threshold of acid-tolerance of the duodenal mucosa is unusually high, as indicated by the fact that from 1800 to 2400 cc. of 0.1 N (0.36 per cent) HCl may be introduced daily at a steady rate for ten days without causing an ulcer, provided an acidosis does not result. This means that, before it may be said that excessive acid secretion *alone* is the cause of an ulcer in a dog, it must be shown that the dog secretes acid above the rate just indicated. Even then, the fact that the ulcer occurs in a circumscribed area shows unequivocally that the factor of a localized area of lowered resistance plays a role. So, a minimum of two factors constantly exists in etiologic considerations of peptic ulcer: one is a *locus minoris resistentiae* and the other is acid.

Acid-Pepsin. Schiffrin and Warren (49) introduced 30 cc. of 3 per cent pepsin in 0.1 N HCl into the stomach of four cats every hour eight times daily; three of the animals developed gastric ulcerations in five to eight days and the fourth showed a small duodenal ulcer after 25 days. Howes et al. (50) observed that acid-pepsin solutions retarded the healing of artificial gastric ulcers in cats to a greater degree than did acid alone. Matzner et al. (51, 52) reported that, in rats fasted two days out of three, the substitution of 0.3 per cent HCl plus 20 per cent pepsin for the drinking water resulted in the development of ulcers of the prostomach in 29 of 30 rats in 12 to 21 days. When the rats were fed ad lib., only two out of ten showed prostomach ulcers.

Application of Acid or Acid-Pepsin to the Intestine

Matthes (60) demonstrated that, when gastric juice was perfused through a loop of jejunum in the dog, necrosis of the superficial cells occurs. This has been confirmed repeatedly. We (61) observed that, in a Thiry fistula of the upper jejunum, bleeding occurs after 15 to 30 minutes of perfusion with 0.1 N HCl. Schiffrin (49,62), using cats, confirmed the observations of Matthes and found that the addition of pepsin to a hydrochloric acid perfusate exaggerated the injury caused by acid, producing deep ulceration and sometimes perforation. His perfusions were conducted for 12 hours and under a pressure of 20 mm. Hg, sufficient to predispose to venous stasis. Schiffrin also studied the threshold of peptic activity necessary to produce ulceration under his experimental conditions. He found that the minimum concentration of pepsin necessary was 0.1 to 0.2 per cent of a 1:10,000 pepsin solution at pH 1.2 to 1.3. Such a solution has an acid and pepsin content comparable to that of the gastric juice secreted by a dog during a meal, and, indeed, Schiffrin was able to produce ulcers

by the use of canine gastric juice instead of the pepsin-HCl mixture. Under the same conditions, the minimum acidity necessary to produce ulceration was found to be about pH 2, or 0.01 N.

Driver and his associates have utilized the perfusion technic to study the factors concerned in the susceptibility of jejunal loops to the action of pepsin solutions. They found (63) that various chemical agents which increase the permeability of the mucosa to protein (e.g., sodium hexametaphosphate, hexylresorcinol) increase the incidence and severity of ulcers. If the permeability was reduced by coating the intestine with mineral oil (64) prior to perfusion, the digestive action was markedly inhibited. Varying the pepsin concentration between 0.1 and 0.2 per cent had no effect on the severity of ulceration (65). The time required for perforation to occur was reduced by raising the hydrostatic pressure of the perfusing fluid (66), an effect which could be counteracted by simultaneously increasing the intraabdominal pressure (67). However, the extent of necrosis was not reduced when the increased intraluminal pressure was opposed by increased intraabdominal pressure. This is to be expected, since under the latter circumstances the embarrassment to the blood supply of the gut would be, if anything, increased. The role of the pressure factor was further illustrated (68) by the finding that pancreatin in sodium bicarbonate produced ulceration in the intestine only when the perfusion was carried out under a pressure equivalent to 90 mm. Hg.

The Gradient of Susceptibility in the Digestive Tract

Although Langenskiold (69) observed in some of his experiments that the jejunum was more readily digested when perfused with juice from a Pavlov pouch than was the duodenum, he considered the difference due to technical errors; he did not, therefore, fully accept Matthes' concept of a gradient of susceptibility to the digestive action of gastric juice. We (70) observed that perfusion of a pouch of the pyloric antrum with 0.1 N HCl, which causes bleeding of a jejunal loop, did not cause bleeding of the pouch. However, if the mucosa of the pouch was massaged to rub off the mucus covering the rosette, which is more subject to trauma, bleeding occurred with 0.1 N HCl but not with gastric juice of the same total acidity.

Mann and Bollman (45) and Florey and Harding (71) demonstrated beyond doubt that the susceptibility of the mucosa to damage by acid increases as the distance from the pylorus is increased. Schiffrin and Warren (49) concluded that the jejunum showed greater resistance to perfusion with 0.1 N HCl than did the duodenum, as judged by the gross appearance of the mucosa. The experiments of Driver et al. (65), in which

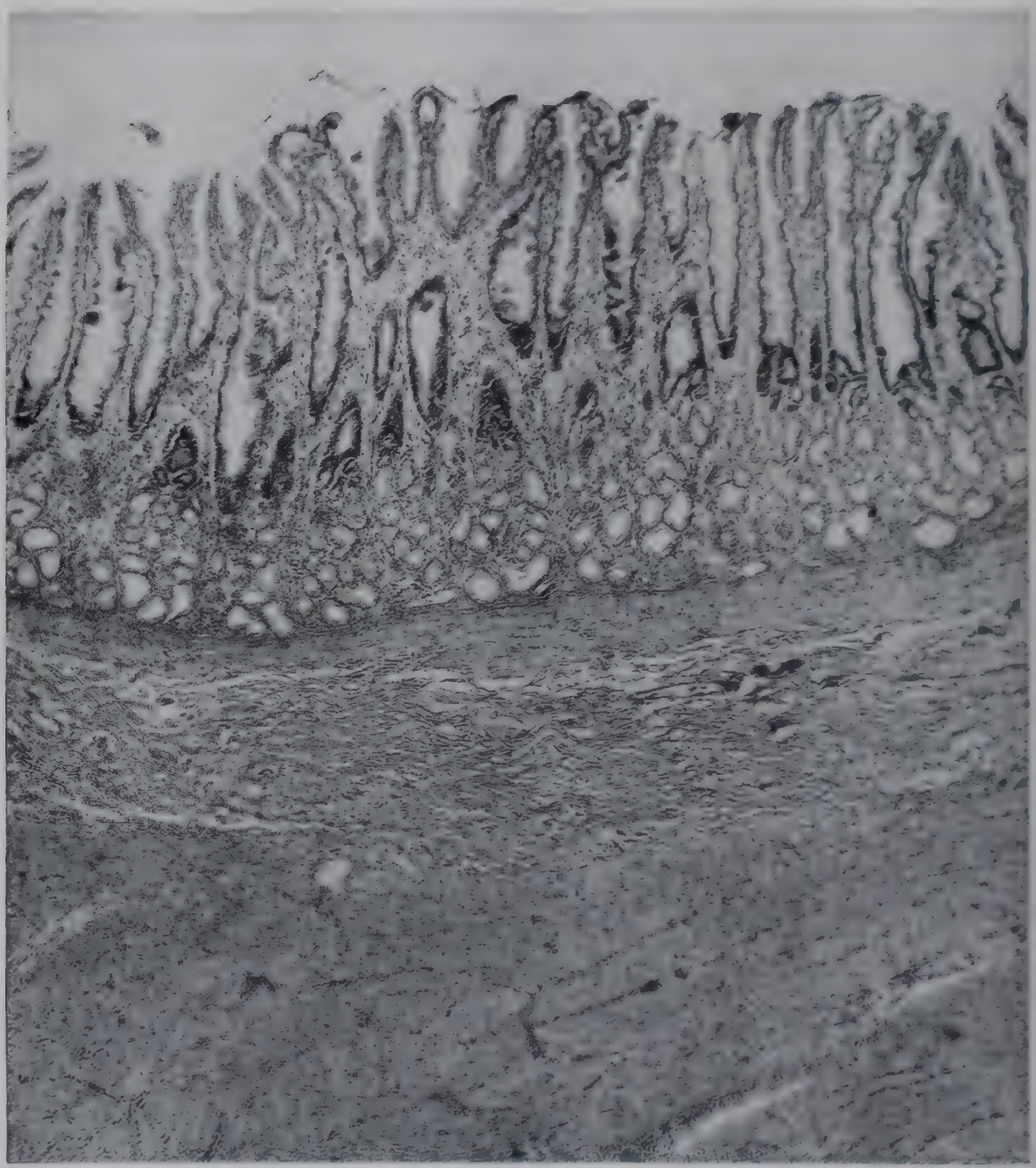


FIG. 51. Appearance of pyloric mucosa after exposure to 0.1 N HCl dropped through a 23 gauge needle for 30 minutes at the rate of 120 drops per minute. The mucous membrane is unaffected.

loops of jejunum at varying levels below the ligament of Treitz were perfused with acid-pepsin, indicated that the more distal loops were more susceptible to ulceration.

More recently, Kolouch (72) allowed a hydrochloric acid solution (pH 1.2), or dog's gastric juice, to drip upon exteriorized segments of the pyloric antrum and duodenum in the dog. He observed that the antral mucosa was decidedly more resistant. This experiment makes an excellent classroom demonstration, especially when segments of the pyloric antrum

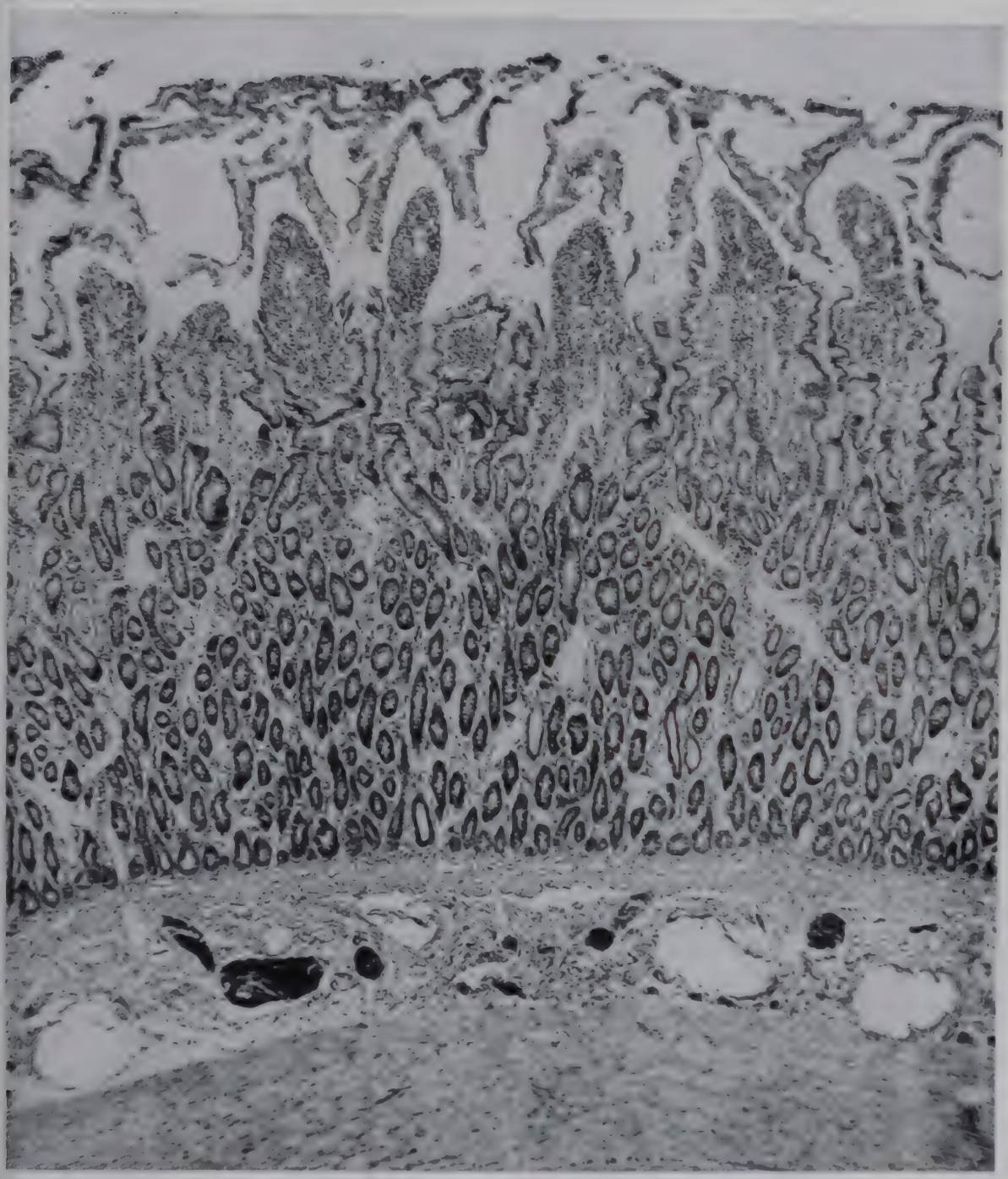


FIG. 52. Appearance of duodenal mucosa after exposure to acid as in figure 51. The tips of the villi are denuded. The surface epithelium is separated in almost solid ranks.

and jejunum are prepared in the anesthetized dog. The jejunum is preferable to the duodenum for comparison because it reacts more quickly to the acid solution. Exposure of the jejunum to 0.05 N HCl for periods as short as ten minutes causes superficial necrosis of the tips of the villi in the anesthetized animal.

Figures 51, 52, and 53 illustrate the gradient of susceptibility as demonstrated by the Kolouch technic.

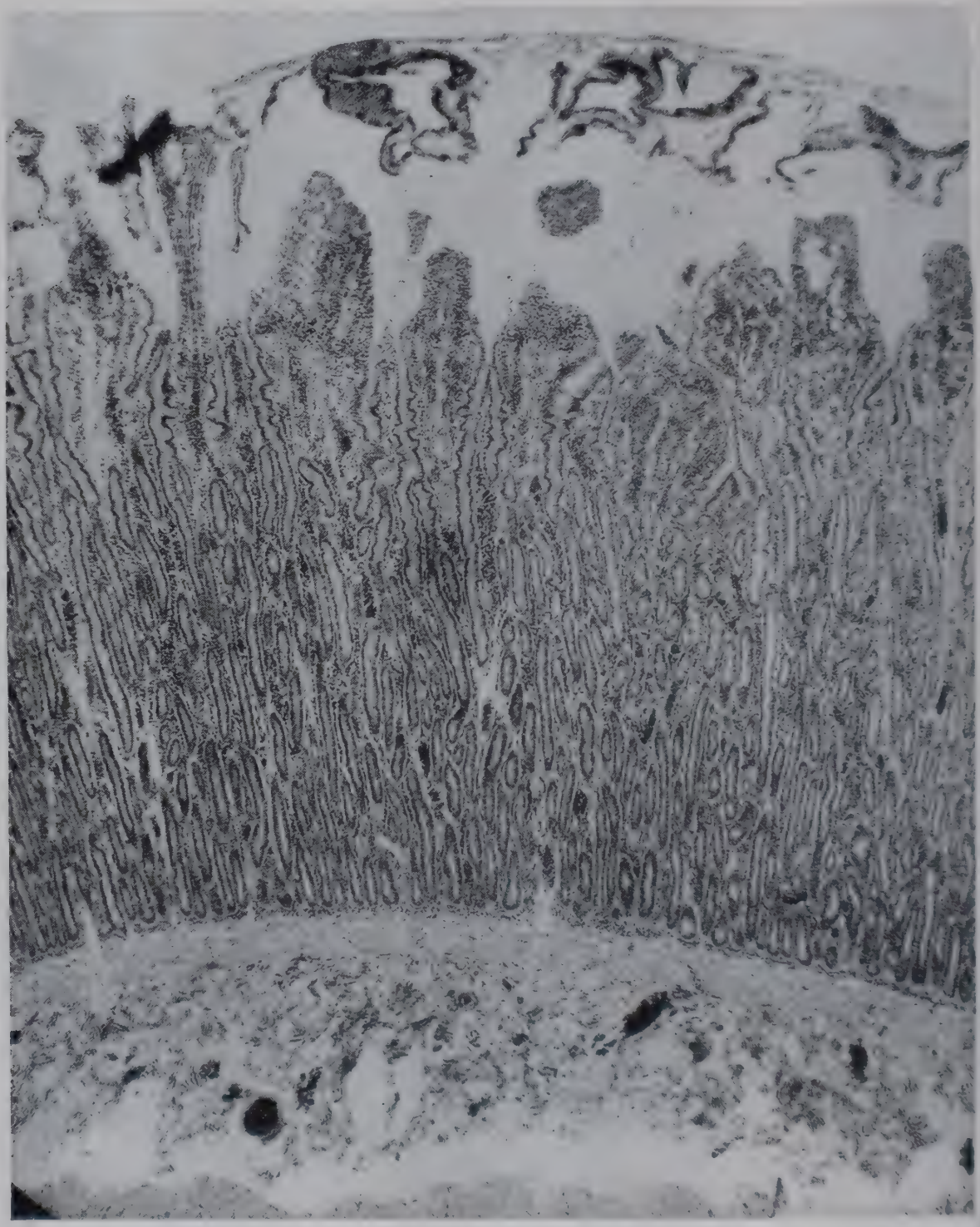


FIG. 53. Appearance of jejunal mucosa after exposure to acid as in figure 51. The epithelial layer is desquamated; the tips of the villi are disrupted and there is marked hyperemia with hemorrhage throughout the mucosal layer.

COMMENT

The foregoing review of experiments with sham-feeding, histamine, and perfusion with acid-pepsin indicates that proof is still lacking that gastric hypersecretion alone initiates the ulcerative process in the intact stomach and duodenum. It appears

from the evidence now at hand that some other factor or factors operate to impair the vitality of the mucosal cells, placing them at the mercy of a digestive juice which they are ordinarily adapted to withstand.

Role of Bile

Biliary Exclusion

Long before the introduction of duodenal drainage operations, it was observed that the exclusion of bile from the duodenum led to the development of chronic duodenal ulcer in a significant percentage of animals. For example, in 1856, Kölliker and Müller (73) observed chronic duodenal ulcers in two of five dogs with gallbladder fistulas. In one dog, which had become icteric due to biliary obstruction, death was caused by perforation of the ulcer. In reviewing the studies on the effects of biliary exclusion on the development of peptic ulcer, it is convenient to group the reports according to the method of excluding the bile from the intestine.

Biliary Obstruction. In the course of some studies on animals with ligated common bile ducts, Popoff (142), in 1880, observed a case of perforated duodenal ulcer in a dog one month and eight days after operation. He considered it unlikely that this was a traumatic ulcer, because it did not occur in any of the remaining animals subjected to an identical procedure. The author quoted Charcot as having made a similar observation in the guinea pig. It is strange that no advantage was taken of these observations for many years, perhaps because the original investigators only mentioned the ulcers as findings incidental to the main purposes of their studies.

In 1914, Gundermann (95) attempted to produce ulcers in rabbits by ligation of the common duct; his four experimental animals survived 18 hours, 30 hours, six days, and eight days respectively, and in the pyloric antrum of the rabbit surviving six days he found an ulcer. Obviously, these animals were not observed for a sufficiently long period of time. The same criticism applies to the experiments of Kleeblatt (110) in the following year. This author performed common duct ligations in 12 dogs, most of which were observed for only a few days, the longest being 24 days. Lesions which the author describes as ulcers were found in the duodenum in 10 of the 12 dogs, but, from the photographs accompanying the article, these lesions were actually simple depressions of the mucosa over lymph follicles, normally found in the duodenum of the dog (see p. 3).

The era of more critical work on the results of biliary obstruction began in 1928 with the report of Hosomi (101), who was interested in the plastic repair of the common duct. He resected 3 cm. of the duct in dogs, and

transplanted into the defect a section of the common carotid artery previously preserved in alcohol 25 days and washed with saline 14 hours preoperatively. The animals developed jaundice in five to seven days, and succumbed after 80 days or longer. Of the 15 dogs reported, three had erosions of the duodenal mucosa, and four had definite ulcers of the duodenum in addition to erosions and petechial hemorrhages in the stomach. The author believed that the lesions were not due solely to the biliary obstruction, but attached greater significance to local factors (such as infection or interference with duodenal function by postoperative adhesions) and to circulatory disturbance.

The most comprehensive study available of the relation of peptic ulcer to experimental biliary obstruction is presented by Bollman and Mann (91). They observed 87 dogs with double ligation and section of the common duct, with the addition of cholecystectomy in most of the animals, and removal of one to three lobes of the liver in several. These dogs were observed over a period of five to 295 days, during which time most of them were on a diet consisting of dog biscuit, milk, and corn syrup, while the remaining animals received a coarser diet of cornmeal, ground bone, and meat scraps. 64 dogs, surviving from the fifth to two hundred and ninety-fifth postoperative day, showed acute, subacute, or chronic peptic ulcer; these included eight cases of gastric ulcer, seven of which were located on the pylorus, and one at the incisura—all on the lesser curvature. The duodenal ulcers were situated 1 cm. beyond the pylorus, slightly anterior to the line of the lesser curvature. Dietary factors were considered to play a definite role, since ulcers developed sooner in dogs on a coarse diet; however, the importance of the actual state of nutrition was questionable, in view of the fact that ulcers were found in animals well-nourished up to a few days before death, while some dogs became cachectic and died without ulcer. It appeared also that the jaundice *per se* was of more significance for the etiology of these lesions than the absence of bile from the intestine, because the authors were unable to prevent the formation of ulcer in jaundiced dogs by feeding gallbladder bile three times daily. Of interest in this regard is the report by Dostal and Andrews (124) of a dog surviving 499 days with complete biliary obstruction; the animal died of hemorrhage from one of four large duodenal ulcers, in addition to which there were numerous small erosions and one ulcer in the stomach.

Halperin (97) reported his observations in nine dogs developing stenosis of the common duct after experimental plastic procedures. Seven of the dogs had ulcers: four duodenal, two gastric, and one both duodenal and gastric. The author ascribed the ulceration to (a) interference with neutralization of the acid chyme and (b) hepatitis, which was invariably present in these animals.

Fiessinger and Palmer (128) obtained duodenal ulcers in one of four dogs, Hawkins and Whipple (99) in two of three dogs, and Iesu (102) in four of six dogs in which the common duct was ligated; the latter author observed his animals from 42 to 81 days. He considered the lesions a result of the alteration in liver function and cholemia. Hebert (100) observed a duodenal ulceration in five of 13 dogs with obstructive jaundice produced by ligation of the common duct, while Salmon (74) reported only one ulcer, gastric in location, in 22 such dogs.

In the rabbit, multiple small superficial ulcerations were noted by Nakashima (132) in 10 of the 15 animals with ligation of the ductus choledochus. The lesions occurred in all parts of the stomach. Blood studies revealed a rapid rise in bile acid content varying from an undeterminable amount to 31.64 mg. per cent within 24 hours, and the surface tension of the blood showed a progressive decrease beginning two hours after operation.

Table 7

INCIDENCE OF ULCER IN DOGS WITH BILIARY OBSTRUCTION

Observer	*Date*	*Number of Dogs*	*Number with Ulcers*
Popoff (142)	1880	1	1 duodenal
Hosomi (101)	1928	15	4 "
Ivy (104)	1931	5	2 "
Bollman (91)	1932	87	56 " 8 gastric
Dostal (124)	1932	1	1 " and "
Halperin (97)	1933	9	4 " 2 " 1 both
Ivy (105)	1933	7	5 " or "
Fiessinger (128)	1935	4	1 "
Hawkins (99)	1935	3	2 "
Iesu (102)	1937	6	4 "
Hebert (100)	1938	13	5 "
Berman (75)	1944	30	8 "
Totals	..	181	104 (57 per cent)

Numerous observations in our laboratory (75, 104, 105), involving a total of 42 dogs with biliary obstruction, completely confirm the experience of Bollman and Mann (91). In dogs surviving up to 77 days with ligated common ducts, we (75) obtained an incidence of 27 per cent duodenal ulcers, while in another, smaller group observed over a longer period (105), gastric and duodenal ulcer occurred in 71 per cent. All of these dogs had hepatitis and cirrhosis. It is clear that the incidence of ulcer increases as the period of observation lengthens.

An approximate figure for the general incidence of peptic ulcer following biliary obstruction was obtained by selecting those data which appear to be based on adequate observation (Table 7).

Biliary Fistula: *External.* Most of the investigators who have studied the effect upon the duodenal mucosa of external loss of bile have utilized the simple method of ligating (and usually sectioning) the choledochus and suturing the opened gallbladder to the skin. This technic has been widely criticized because it predisposes to ascending infection of the biliary tract, and in recent years has been supplanted by the improved technic originated by Rous and McMaster (145).

Apparently the first observations on cholecystostomized choledochus-ligated dogs were those of Langenskiold (69), whose intention it was to exclude both bile and pancreatic juice from the duodenum, but this was obviously not accomplished in view of the fact that he left the lesser pancreatic duct intact. Neither of his two dogs, which survived 15 and 26 days respectively, showed any changes in the duodenum.

In their description of a method for the sterile drainage of the bile, Rous and McMaster (145) state that 17 dogs had biliary drainage periods up to three months, but they make no mention of the occurrence of ulcer. However, Berg et al. (87) used this method of bile drainage in nine dogs and found acute, subacute, and chronic duodenal ulcers in seven cases, with additional ulceration of the stomach (lesser curvature) in two of the dogs. The animals were examined at intervals from 12 to 46 days; ulcers were absent only in two dogs autopsied on the twelfth and fifteenth post-operative days. Berg and Jobling (86) found further that the care and surroundings of the animals influenced to a significant extent the frequency of ulcer in biliary fistula dogs. For example, the incidence of peptic ulcer decreased from 100 per cent to 30 per cent when the experiments were carried out in new quarters which supplied better living conditions for the animals.

Choledochostomy was performed in seven dogs by Loewy (114), but the internal flow of bile was reëstablished in three; the remaining four dogs were observed for from 19 to 47 days, and only the longest surviving animal had an ulcer of the duodenum; the remaining three had considerable duodenitis. From these findings the author concluded that complete biliary exclusion causes duodenitis and, occasionally, ulcer.

Puestow (143) studied a series of dogs with exteriorization of the segment of the duodenum containing the orifice of the common duct. No mention is made of the occurrence of peptic ulcers, but the author is quoted by Blanck (89) as having stated in a personal communication that several of the animals died rather suddenly with perforated peptic ulcers. The animals which remained healthy were frequently observed to lick bile from their fistulas.

Pecco (141) produced acute, subacute, and chronic duodenal ulcers in three of eight choledochus-ligated cholescystostomized dogs surviving from several months to one year, but Amorosi (82), using the same method, found only a moderate inflammation of the gastric and duodenal mucosa in six dogs living five months, with well-marked generalized degeneration of the hepatic cells present at autopsy. Pecco showed that the ulcers in his dogs were not due to trauma, since no ulceration occurred in four dogs in which he simply sectioned the duodenum between clamps and performed an immediate anastomosis. Determinations of gastric acidity revealed no consistent change from the preoperative values (no data are given).

In ten dogs with external biliary drainage, De Vincentiis (76) observed six instances of ulcer. In reports of experiments with five dogs observed from approximately two weeks to five months after production of biliary fistulas, cholecystostomy, and choledochus-ligation, true chronic peptic ulcer was noted by neither Pagliani (140) nor Donati and Cavazza (123), yet the latter investigators concluded that they were "able to produce ulcerative lesions of the gastric and duodenal mucosa with all the anatomic characteristics of peptic ulcer of man." According to Hawkins and Whipple (99), who used various methods of biliary drainage, duodenal ulcers are relatively common in biliary fistula dogs. They found ulcers of the duodenum in seven of the 30 dogs which lived more than three months after operation; one of the animals died of massive hemorrhage, another of perforation. It was their impression, however, that ulceration in fistula dogs is not so frequent as in those with biliary obstruction.

It is reasonable to assume that dogs surviving for long periods of time with external biliary fistulas are not completely deprived of bile inasmuch as the animals are able, with the type of drainage heretofore employed in most of the studies, to lick the secretions from the fistula. Blanck (89) examined the importance of this factor in a controlled experimental study. He made biliary fistulas of the Rous-McMaster type in eight dogs, five of which served as controls, while in the remaining three the bile was collected from the fistulas in a sterile balloon and returned by mouth. Unfortunately, the dogs all died within 24 days after operation, and the bile-fed dogs did not differ significantly from the controls; no chronic ulcers were observed. Nevertheless, the author concluded that bile feeding prevents ulceration in these dogs.

We (84) returned the bile to the duodenum in 15 dogs with external fistula which survived from 16 to 175 days. Chronic ulcers of the duodenum occurred in only two dogs; in both of these the ulcer was directly responsible for death by perforation into the peritoneal cavity. It is interesting that in these two dogs the bile was returned via a long rubber tube passing through the common bile duct and terminating in the small intestine about 50 cm. distal to the papilla of Vater.

It is interesting that Brunschwig et al. (93) found no changes in the liver and no gastrointestinal ulceration after prolonged biliary drainage through a Dragstedt cannula, even in the presence of advanced cachexia; prior to the use of this technic they had found duodenal ulcers to be "distressingly frequent" (88). According to the authors, the results might be attributed to the elimination of liver infection made possible by the Dragstedt method. The possibility must be considered that ulcers do not occur when the bile passes over the intestinal mucosa, even when this mucosa is isolated from the remainder of the intestine.

Cholecystostomy and choledochus-ligation was performed by Cornil et al. (120) in seven dogs, four of which died spontaneously from the fifteenth day to the third month after operation, while the remaining three were sacrificed at similar time intervals. One dog had a large ulcer at the pyloroduodenal junction (16 days); a similar lesion was found in a dog sacrificed after three months, while one living six weeks had two superficial duodenal ulcers.

Hanke (98) instituted external biliary drainage via the gallbladder or cystic duct in seven choledochus-ligated dogs. The animals survived from 19 to 85 days, and all had lesions of the duodenum, varying from erosions to multiple deep ulcers with perforation. In some of the animals, lesions were present in the stomach, especially in the pyloric region. All of the lesions were, according to the author, true peptic ulcers brought about by the relative predominance of acid digestive secretions in the absence of the neutralizing action of bile.

We (109) were able to prevent ulceration in 17 biliary fistula dogs of the Rous-McMaster type by feeding 15 Gm. of mucin twice daily, whereas six of the ten control dogs developed ulcers. It was further shown (184)

Table 8

INCIDENCE OF ULCER IN DOGS WITH EXTERNAL BILIARY FISTULA

Observers	*Date*	*Number of Dogs*	*Number with Ulcers*
Berg (87)	1927	9	5 duodenal, 2 gastric and duodenal
Pecco (141)	1931	8	3 "
Kim (109)	1931	10	6 "
Amorosi (82)	1933	6	0 "
Loewy (116)	1935	4	1 "
Hawkins (99)	1935	30	7 "
Bissell (88)	1936	30	0
Totals	..	97	24 (25%)

that alkalies (1 Gm. each of sodium bicarbonate and calcium carbonate) were equally effective in the prevention of ulcer in biliary fistula dogs. The average weight loss was less, however, in the mucin-treated group than in the alkali-treated and control groups.

Table 8 summarizes the incidence of ulcer following external biliary drainage, including only those reports which appear to be of significance.

Internal. It has been pointed out by many investigators that external drainage of the bile predisposes to infection of the biliary passages and the liver. The same criticism may be applied to the internal drainage of the bile when the latter is accomplished by anastomosing some part of the biliary tract to the digestive tube. This method has the advantage, however, that, if an unobstructed anastomosis is obtained sufficiently low in the gastrointestinal tract to prevent regurgitation and to minimize absorption, a relatively complete loss of bile to the organism is assured. Furthermore, this method has seemed most logical to a number of investigators wishing to compare the relative protective role played by bile and pancreatic juice in the genesis of ulcer following duodenal drainage.

Weiss and Hubster (156) ligated the common duct and anastomosed the gallbladder to the terminal ileum in four dogs; one lived eight days, the others four to five months, and at autopsy all had acute gastritis and duodenitis. Weiss and Gurriaran (155) mention the occurrence of an ulcer in one of three dogs subjected to the above operation, but whether they are referring to the same dogs or a different series is not clear. The same uncertainty exists concerning the incidence of duodenal ulcer following cholecysto-ileostomy in the dogs described by Deloyers and associates (121, 134, 135, 136). It is variously reported as four in seven (drainage 100 cm. proximal to cecum), six in seven (drainage 80 cm. proximal to cecum), five in eight, and six in eight. If these are four distinct series, which is doubtful, the incidence of ulceration following internal biliary drainage would appear to be very high.

Deloyers (121) reports further that choledocho-ileostomy in 11 dogs, in five of which the gallbladder was removed, resulted in only one ulcer during a period of 21 to 245 days. This is explained by the fact that choledocho-ileostomy, as contrasted with cholecysto-ileostomy, leads to biliary obstruction as a result of cicatricial contraction of the small anastomotic opening; thus, the bile is retained, instead of being lost.

Cholecystojejunostomy, with the site of drainage 45 cm. distal to the ligament of Treitz, was carried out in five dogs by Owings and Smith (139); two of the dogs developed ulcers in 76 and 119 days respectively, and the remaining three continued in good health until sacrificed; no ulcers were present. With the same operation, Graves (96) obtained one case of ulcer in 15 dogs.

Just as the technic of Rous and McMaster reduced or eliminated the factor of infection in external biliary drainage, so the method of Kapsinow (108) obviated the possibility of ascending infection in internal drainage. This investigator anastomosed the gallbladder to the pelvis of the right kidney, and ligated the common bile duct. Of 43 dogs in this series, 17 developed typical duodenal ulcer in the vicinity of the ampulla of Vater. This excellent report contributes strong evidence to the importance of bile loss in the etiology of experimental ulcer. It is confirmed by the work of Loewy (115), who found duodenal ulcers in two of three dogs surviving a significant length of time after anastomosis of the common duct to the right ureter. The author's figures of gastric acidity, do not, unfortunately, contribute further to the problem, inasmuch as he compared the secretion of one normal dog with two operated dogs; however, he believes that faulty neutralization plays an important role. *More recently, Scott (77) was able to maintain four dogs with total biliary fistula into the renal pelvis for from 16 months to three and one-half years by administering the fat-soluble vitamins parenterally. None of these dogs developed ulcer.*

Table 9

INCIDENCE OF ULCER IN DOGS WITH INTERNAL BILIARY FISTULA

Observer	*Date*	*Number of Dogs*	*Number with Ulcers*
Kapsinow (108)	1926	43	17 duodenal
Weiss (155)	1930	3	1 "
Loewy (114)	1930	3	2 "
Owings (139)	1932	5	2 "
Graves (96)	1935	15	1 "
Deloyers (121)	1936	8	6 "
Scott (77)	1945	4	0
Totals	..	81	29 (39%)

While studying the results of cholecystoduodenostomy, we (146) anastomosed the gallbladder to the upper duodenum, ligated the common duct, and performed a gastroenterostomy with pyloric exclusion. The occurrence of jejunal ulcer in five of the 14 dogs subjected to this procedure may have been due in part to the biliary and hepatic disturbance which was present. However, the same incidence of jejunal ulcer might have been obtained as a result of the gastroenterostomy with exclusion (see p. 319).

A tabulation of the results of internal biliary drainage is given in Table 9.

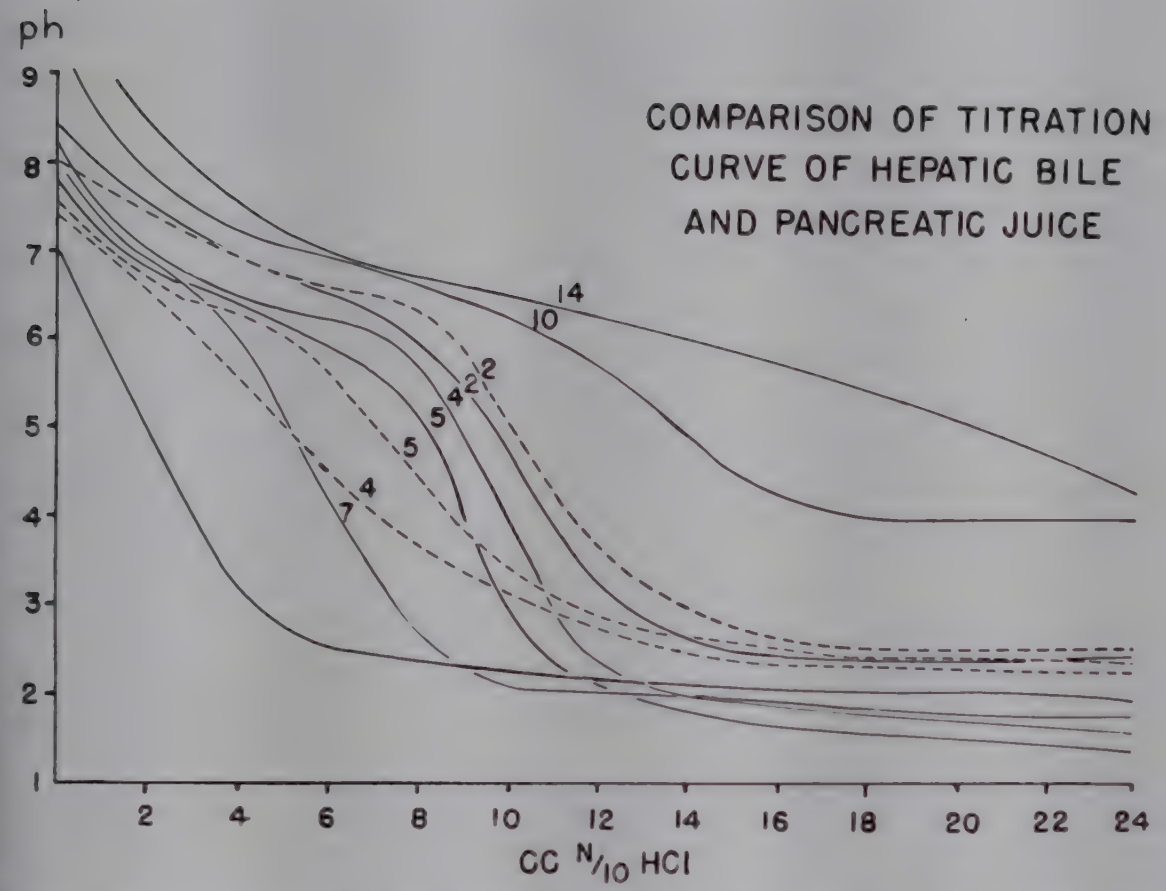


FIG. 54. Comparison of the buffer value of hepatic bile and pancreatic juice. The solid lines represent bile and the dotted lines pancreatic juice from the same dog. The lowest line is gallbladder bile. The numbers on the lines refer to the day after operation on which the secretions were collected. The 24-hour volumes were measured and 10 cc. amounts titrated with 0.1 N HCl, and the corresponding pH determined with the quinhydrone electrode.

MECHANISM OF ULCER FORMATION FOLLOWING BILIARY EXCLUSION

Most of the speculation on the cause of ulcer formation following exclusion of bile from the intestine has been based on the premise that the neutralization of acid gastric juice is impaired by removal of one of the alkaline constituents of the duodenal contents. This argument presupposes that bile plays an important part in reducing the acidity of the chyme as it enters the duodenum, and that it may also affect the intragastric acidity by regurgitation into the stomach. However, this is only one of several factors which require consideration.*

NEUTRALIZING CAPACITY OF BILE. It has been established, by pH determinations on the bile of the dog (85, 103, 122, 125, 127, 130, 133, 152), as well as the human (92, 112, 130, 133, 144, 152), that bile is approximately neutral; liver bile is slightly alkaline, whereas gallbladder bile is neutral or slightly acid. However, to assume, as some authors have

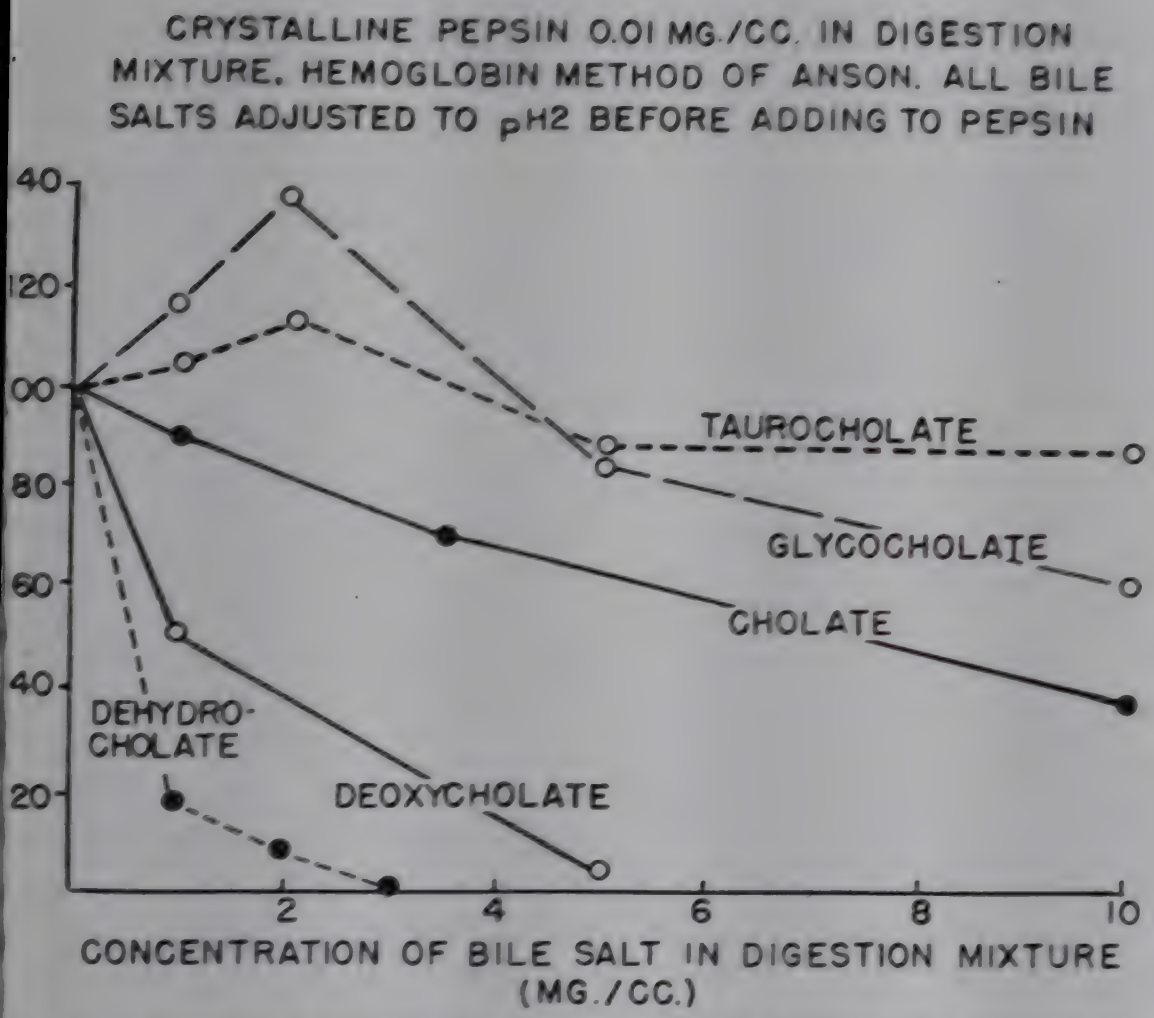
* See Bissell and Andrews (88) for a detailed analysis of the factors concerned in acholic cachexia.

on the basis of this fact, that the bile has a negligible buffer value, a erroneous. Jones (107) has shown that hepatic bile may occasionally be a alkaline or even more alkaline than pancreatic juice; and his data (Fig. 54 nullify the significance of reports that it requires nine volumes of bile t raise the pH of HCl from 1.6 to 6.2 (119), or that bile neutralizes gastri juice in a volume ratio of about 30 to 1 (128). Bogoras (90) has shown tha while cholecystogastrostomy produces only a slight decrease in the tot acidity of the gastric juice, the free acid is markedly reduced, so that t bile appears to be efficient in buffering free acid. The data of Enderle et al. (126), purporting to show that the pH of the gastric juice is u changed by draining the bile into the stomach, are meager because on one dog was studied.

Changes in the Acidity of the Upper Digestive Tract Followin Biliary Exclusion. The evidence indicates that the pH of the duoden contents is not significantly altered by the absence of bile. This is agree upon by three investigators, all using fistulas of intestinal loops to obta duodenal contents before and after exclusion of the bile. Hebert (10 found that the alkalinity of the duodenal content was not materia changed by biliary obstruction (ligation of common duct), although t buffering capacity was definitely reduced. McRoberts (117) could fi no constant change in pH of the duodenum after external biliary dra age; in fact, Loewy (116) presents data showing that under these co ditions the content at the duodenojejunal angle was actually more alkal

In the light of the above studies, it is interesting that Simnitzky (1 and Selesnjew (148) both found an increased output of gastric juice response to test meals in jaundiced dogs. Still and Carlson (153) stud the gastric secretion in acute and chronic jaundice in Pavlov pouch do they found that acute or temporary jaundice, produced by intraven injection of bile, markedly lowered the gastric acid, while in chro jaundice following duct ligation the acidity following a test meal w raised but the volume of secretion was diminished. The authors sugge that in obstructive jaundice there may be enough bile acids in the bloo have a significant cytolytic action on the acid secreting cells, causing increased excitability of those cells. It is significant that Hebert (1 Selesnjew (148), and Still and Carlson (153) are agreed that the res gastric acidity is definitely increased over the control values. In cont with the other investigators, however, Hebert (100) could detect significant change in the stimulated gastric secretion in dogs with a ga fistula.

Due consideration must be accorded the report of Jarno (78), c firmed by Driver and Carmichael (79), that bile salts inhibit pe activity. We have found that sodium taurocholate and sodium glycoch



IG. 55. The effect of various bile salts upon peptic digestion of a hemoglobin rate. The sodium salts of taurocholic and glycocholic acid are soluble at pH 2 the other bile salts are precipitated out at this pH.

ow concentrations markedly enhance peptic activity but in high con- trations inhibition occurs (Fig. 55). Mixtures of human hepatic bile human gastric juice show the same phenomenon: low concentrations ile enhance the peptic activity whereas high concentrations inhibit 3).

Effect of Neutralization Therapy in Biliary Exclusion. As has ady been pointed out, we (109, 184) have been able to prevent ulcers iliary fistula dogs by the administration of alkalies or mucin. One ticularly interesting observation illustrated the efficacy of mucin in respect: one of our dogs developed jaundice and a huge ascites plus nite symptoms of ulcer, seven months after a plastic repair of the com- n duct which resulted in biliary obstruction. Mucin feedings were un, and within one month the ascites disappeared and blood was no ger present in the stools; the dog appeared in excellent health. When cin was discontinued, the ascites and tarry stools recurred, to be re- d once again with feedings of mucin. At death, the dog was found to

be moderately ascitic; two healing ulcers were present in the duodenum. This was later observed in two additional dogs. These findings do not necessarily support the opinion (86, 118) that bile supplies to the diseased area a reinforcement of mucin derived from the mucosa of the gallbladder, since bile contains very little true mucin. Perhaps the fact that gastric mucin has a combined buffering and protective action explains why we found it to be even more efficient than alkali in maintaining the health of biliary fistula dogs. It must also be kept in mind that mucin may have some as yet unknown relationship to the function of the liver (see p. 295).

Loss of the Digestive Function of Bile. It has been suggested that, since the bile plays a vital role in digestion, its simple absence from the intestine may account for the lesions. Bollman and Mann (91) attempted unsuccessfully to prevent the ulcers in jaundiced dogs by administration of bile salts twice daily. Oda (137) fed ox gall to rabbits with artificially produced gastric mucosal lesions, and found that healing was delayed; he construed this as evidence that, if bile is successfully used in treating peptic ulcer, its action cannot be ascribed to neutralization. We (84), however, have shown that, in dogs with external biliary fistulas of the Rous-McMaster type, the return of the dogs' own bile into the intestine or the feeding of ox-bile salts by mouth, will prevent ulcer and maintain the dogs in normal health. This is not, of course, in contradiction to the findings of Bollman and Mann, because the latter were dealing with jaundiced dogs. That the obstruction of the bile ducts superimposes some additional factor over exclusion by sterile drainage is obvious from the accompanying comparison of the collected data on the incidence of ulcer following various types of exclusion.

Procedure	*Number of Dogs*	*Number with Ulcers*	*Incidence*
Biliary obstruction	181	104	57%
External biliary drainage	97	24	25%
Internal biliary drainage	81	29	36%

Since bile salts play a significant role in the absorption of the fat-soluble vitamins, Scott's (77) observations are of interest and should be extended to include more animals.

Toxic Action of Retained Bile. The concept that the bile salts exert a toxic action on the cells of the upper digestive tract has never received adequate study, although the possibility of such action was suggested by observations (80, 81) reported as early as 1863.

In 1909, Sellards (149) found that the injection of 0.1 Gm. of sodium glycocholate intraperitoneally into guinea pigs resulted in hemorrhage and ulceration of the gastric mucosa; in one guinea pig of his series there was ulceration and perforation of the duodenum. In the dose given, the bile salts caused death in 8 to 15 hours. The author's findings were confirmed by Anderson and Farmer (83), who observed that, in guinea pigs injected with bile salts, the adrenal glands showed a decreased reducing power with silver nitrate; rats, on the other hand, when injected with comparable doses, had no alterations in the gastroduodenal mucosa nor in the reducing power of the adrenals. The latter phenomenon depends largely on the presence of vitamin C in the adrenal glands; it is known that rats synthesize this vitamin, whereas guinea pigs do not. It was noted by Tsuruta (154) that the concomitant injection of various liquids inhibited the ulcer-producing action of bile salts in guinea pigs.

Yoshitomi (157) found that when the circulation of the isolated rabbit stomach was perfused with a solution containing 1/5,000 M. of sodium taurocholate, ulcerations resulted if the gastric contents were acid. This was confirmed by Fujioka (129), who stated that bile acids could also produce ulcers by direct contact with the gastric mucosa; normally, ulceration is not produced by regurgitated bile because the mucus of the stomach is strongly inhibitory. This view is identical with that suggested by Smith (151) many years previously.

Other Factors. It occurred to Schnitker and Emery (188) that perhaps the loss of bile might lead to ulcers by a disturbance in fat metabolism, which would alter the cell resistance because of insufficient lipids in the cell membrane. They analyzed the blood for fat after the ingestion of 500 cc. of cream, but could observe no difference between ulcer patients and controls. In the same connection, Jergesen and Simonds (106) found the blood lipase content of ulcer patients to be higher than that of normals in 76 per cent of 50 patients.

According to Cardia (94), Baggio found typical gastric ulcers in a dog dying 22 days after the introduction of 11 small stones into the gallbladder. The experiment was repeated by Cardia (94) in 12 dogs, with studies of the gastric acidity before and after the operation. Fluoroscopic examinations were made, to follow any changes in the gastric function. The author stated that the gastric secretion and motility in all dogs was increased up to about the tenth month, then decreased to or below the control level. One of the dogs died on the twenty-fourth postoperative day with acute ulcerations of the antrum; another died on the eighty-ninth day, with no ulcers; the remaining dogs were sacrificed at intervals from 10 months to two years, and in no case was an ulcer present. The stones were found lying free in the gallbladder; none of the dogs was jaundiced.

Walsh (138) introduced gallstones into the gallbladder of many dogs without observing the development of ulcer. The dogs remained in excellent nutritional condition and the gallstones were dissolved.

Comment

It has been reasonably well established that when biliary exclusion is complicated by jaundice, the incidence of ulcer is appreciably higher than that following exclusion by biliary drainage, either external or internal. This may mean (a) that the decreased resistance of the mucosa deprived of bile is further diminished by the presence of bile in the tissues and blood; or (b) that the circulating bile produces changes in gastric motility and secretion which throw an excessive burden on the mucosa; or (c) that the incidence of ulcer increases with the time of survival, and therefore the difference is more apparent than real.

Possibility (a) has not received sufficient experimental attention to permit its proper evaluation. With regard to the second possibility—i.e., increased gastric motility and secretion resulting from cholemia—such might be expected to occur on the basis of vagal irritation, which is responsible in part for the bradycardia sometimes observed in jaundice. One observer (150) has reported, for instance, that ligation of the common duct in Pavlov pouch dogs is followed by an increase in the psychic secretion. Also, in support of this point, is the evidence, though unsatisfactory, that experimental biliary obstruction is followed by increased gastric secretion or acidity, or both. However, we do not have any good data on the gastric function in biliary fistula animals. Similarly, we know that alkalies or mucin will prevent the appearance of ulcers after biliary drainage, but we have no information whether the same amounts of buffering substances are equally effective in biliary obstruction; nor can we hazard a guess on the latter point in the absence of data on the gastric secretion following external biliary drainage. On the other hand, if, as the consensus of reports indicates, the upper intestine can maintain its normal pH in the absence of bile, then the basic difficulty is not an excess acidity but a decreased resistance of the mucosa. But then again, one must accord due consideration to the increased fasting gastric secretion shown to be present in experimental biliary obstruction.

As to the third possible explanation, there are two points against the likelihood that the higher incidence of ulcer in biliary obstruction is due to the longer survival. First, the oral administration of bile will prolong life and prevent ulcers during the loss of bile via a fistula, whereas the only evidence available indicates that bile salts do not prevent ulcers in experimental jaundice. Therefore some other factor besides longevity must be concerned. Secondly, Scott (77) kept four internal fistula dogs

and Bissell and Andrews (88) four external fistula dogs, alive without ulcer far beyond the period when obstructed dogs develop ulcers.

The principal conclusion to be reached from the foregoing discussion is that we lack sufficient information on this problem to reach any conclusions. Among the experiments which need to be carried out, we would suggest the following:

1. A comparison of the effects of biliary drainage and of biliary obstruction on gastric motility and secretion: in the experiments on obstruction it would be desirable later to eliminate the vagi.

2. Production of obstructive jaundice in fundusectomized or gastrectomized dogs.

3. Analysis of all data obtained following biliary exclusion to determine whether there is any considerable difference in the measurable effects of exclusion on those animals which develop ulcer as compared with those which do not within a given period of time.

Role of Pancreatic Secretion

As was the case with bile, the role of pancreatic juice in peptic ulcer has been studied by observing the changes following exclusion of the pancreatic secretion from the intestine; this has been accomplished by suppression of the pancreatic juice (ligation of the ducts or pancreatectomy) or by diversion, either external or internal, of the pancreatic secretion.

Suppression of Pancreatic Juice

A diminution or absence of pancreatic secretion as a contributory cause of ulcer was apparently first investigated by Jona (172), who proposed the theory that in ulcer patients there existed a deficiency in the formation of secretin, or an inhibition of its action. He put this theory to the experimental test by ligating the pancreatic ducts in dogs. "In some dogs, both pancreatic ducts were tied and in others only the main pancreatic duct was either simply tied with silk or stout thread, or double tied and cut between ligatures. The animals in the former case, as a rule, died in a few days. This was probably due to some involvement of the bile duct, judging from the animals' appearance." The author claims to have found duodenal ulcers in a "number of animals" thus treated. We doubt whether the structures he calls ulcers were actually ulcers.

We (104) reported duodenal ulcers in six of 61 dogs with ligated pancreatic ducts. In a series of five dogs with the same operation, Berg and Zucker (160) found no ulcers in an observation period extending from 3 to 97 days. Bauer and Aron (158) mentioned one dog in which the external pancreatic secretion was suppressed by subtotal pancreatectomy;

at laparotomy two months later the duodenum was normal. With complete pancreatectomy, Berg (159) found no duodenal lesions in eight dogs from 61 to 270 days after operation. No ulceration occurred in one duct-ligated dog reported by Loewy (116) or in the five dogs studied by Boyce and McFetridge (161) for from eight weeks to 20 months. In a series of 19 dogs with the pancreas completely separated from the duodenum, autopsied from 21 to 720 days after operation, we (84) found only one case of duodenal ulcer.

It is obvious from the foregoing résumé that most of the authors reporting on the incidence of ulcer following the suppression of pancreatic juice were dealing with a small series of dogs. If we sum up this data in tabular form, the low incidence of ulcer in the absence of the external pancreatic secretion is at once obvious. (See Table 10.)

Table 10

INCIDENCE OF ULCER FOLLOWING SUPPRESSION OF PANCREATIC JUICE

Observers	*Date*	*Number of Dogs*	*Number with Ulcer*
Ivy (104)	1931	61	6
Berg (160)	1932	5	0
Bauer (158)	1933	1	0
Berg (159)	1934	8	0
Loewy (116)	1935	1	0
Boyce (161)	1938	5	0
Bachrach (84)	1938	19	1
Totals	..	100	7 (7%)

EXTERNAL PANCREATIC FISTULA

There is a sharp disagreement between the reports of Elman and associates (163, 165, 166) and those of Berg (159, 160) on the occurrence of ulceration following external pancreatic fistula. According to Elman, "peptic ulcers were found uniformly in dogs losing the total external secretion of the pancreas for two weeks or longer." For example, in dogs surviving from six to eight days with pancreatic fistulas, autopsy findings showed hyperemia and small erosions or ulcerations of the gastric mucous membrane, whereas six dogs which were kept alive for at least 13 days by daily injections of 500 cc. of physiologic salt solution all had large duodenal ulcers with no evidence of healing; the general condition of these dogs was good, although vomiting sometimes occurred. As far as Elman is con-

cerned, the ulcers are due to absence of neutralization of the gastric contents, and the pancreatic juice is much more important than bile in this respect. Matthews and Dragstedt (7) stated that duodenal ulcers regularly appeared in dogs prepared with pancreatic fistulas according to the method of Dragstedt, Montgomery and Ellis (178) (Fig. 56). Formation of these ulcers could be prevented for periods as long as six

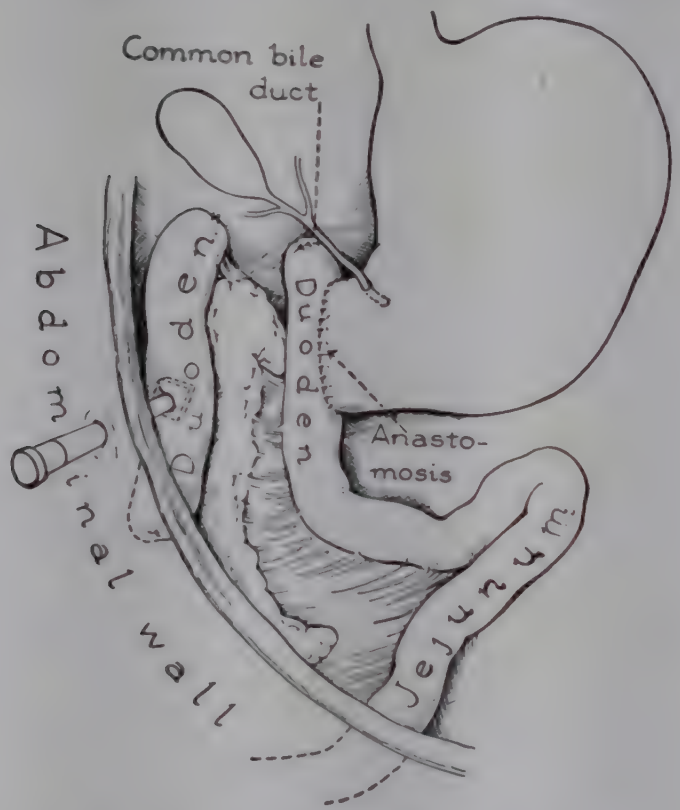


FIG. 56. External pancreatic fistula. Method of Dragstedt et al. (Redrawn from *Proc. Soc. Exper. Biol. & Med.*, **28**: 109, 1930.)

months by the oral administration of calcium carbonate, sodium bicarbonate, or finely ground bone meal.

Berg (159) was able to keep dogs with pancreatic fistulas alive for as long as 37 days by the administration of sodium chloride. In 16 of these dogs surviving from 12 to 37 days, ulcers occurred in only one dog; this dog had jaundice and marked degenerative changes in the liver. The author therefore considers that the absence of neutralization is not an important factor in ulcer formation.

INTERNAL PANCREATIC FISTULA

The opinion of Berg is supported by the meager data available on internal pancreatic drainage (Fig. 57). Deloyers (121) transplanted the

main pancreatic duct into the terminal ileum and ligated the accessory duct; five dogs survived this operation from five to ten months, and only one presented a small superficial ulceration. The same operation was performed by Owings and Smith (139) in an undesignated number of dogs, except that the pancreatic juice was drained into the jejunum 18 inches distal to the ligament of Treitz; exploration of the duodenum at intervals up to 123 days revealed no ulcers. With a similar procedure, Graves (96)

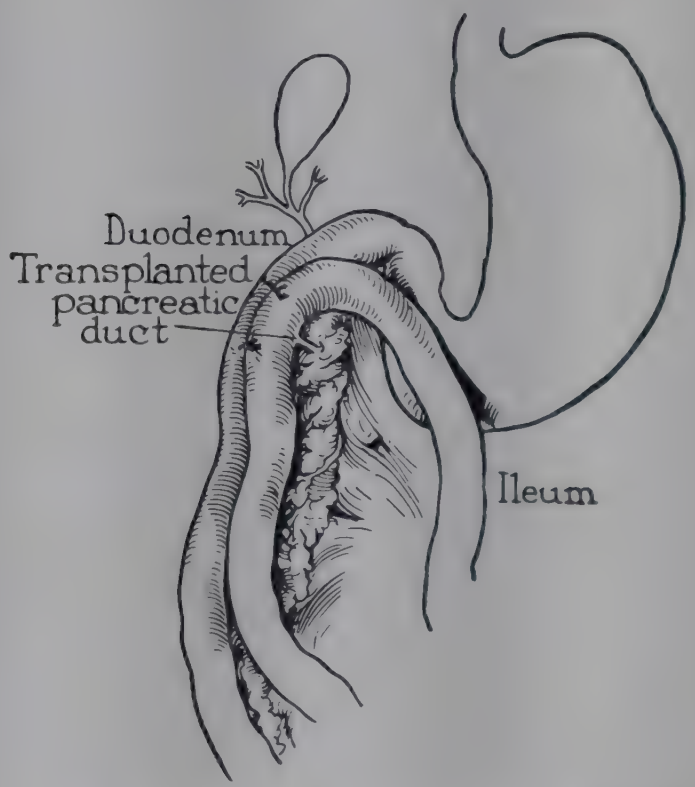


FIG. 57. Drawing illustrating the deviation of pancreatic juice into the terminal portion of the jejunum by transplantation of the main pancreatic duct into the jejunum. (Courtesy, Graves: *Arch. Surg.*, **30:** 833, 1935.)

could produce no ulcers in 12 dogs, some observed for as long as fou months. Working in our laboratory, Craft (162) found no ulcers in si complete pancreatic fistula dogs surviving 16 to 30 days with return o the secretions into the lower intestine.

Loewy (173, 174) described a technic for the drainage of the tot pancreatic juice into the ureter; four dogs with this operation survive from 16 to 37 days. The author states that in the duodenum of one do there was a lesion which had the gross appearance of an ulcer, but th histologic examination made this doubtful; the remaining three anima had no ulcers. Loewy also had one dog with external pancreatic drainag receiving Ringer's solution daily for 32 days; no ulcer was present.

Because of the limited amount of data available, and because of the divergent reports on the subject, it is not possible to estimate the probable incidence of peptic ulcer following pancreatic fistula.

Comment

Observations on the physiology of the upper gastrointestinal tract following pancreatic exclusion are of interest in comparison with the changes previously shown to follow exclusion of bile. Regarding the gastric secretion, Steinberg (176) reported that removal of the pancreas was followed by an increase in the duration and amount, but no significant

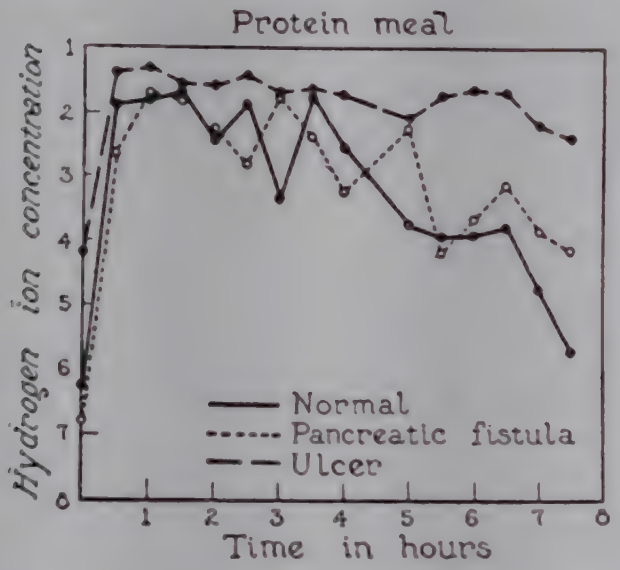


Fig. 58. Variations in pH of the gastric content after a protein meal before and after a pancreatic fistula and during or after the development of a duodenal ulcer. (Courtesy, Hoerner: *Am. J. Digest. Dis. & Nutrition*, **2**: 302, 1935–36.)

change in acidity; he attributed the results to prolonged pyloric spasm, but, in our (167) experiments, gastric emptying was actually more rapid following pancreatectomy. Following ligation of the pancreatic ducts, we (167) observed a temporary decrease in gastric secretion, followed by an increase which in some cases lasted several months, and, in others, a few weeks; the acidity was not materially elevated. These findings confirmed the less extensive studies of Yesko (177). Working with pancreatic fistula dogs, Hoerner (168) demonstrated that there was no marked change in the reaction of the gastric content during fasting or after various types of test meal (Fig. 58). Elman (164) found, however, that acid solutions introduced into the stomach were not so well neutralized by pancreatic fistula dogs as by normals, and that the acidity of the gastric contents was much

higher in fistula dogs than in controls. He believed, therefore, that the hyperacidity frequently found in cases of peptic ulcer may be due, in part, to variations in the degree of regurgitation of pancreatic juice into the stomach.

Jones (107) demonstrated that the buffering capacity of pancreatic juice is about the same as that of hepatic bile (although it may at times be less), but because the amount of pancreatic juice secreted is usually greater than the amount of bile, the total buffer available in the pancreatic secretion is greater. According to Hoerner (171), pancreatic juice collected

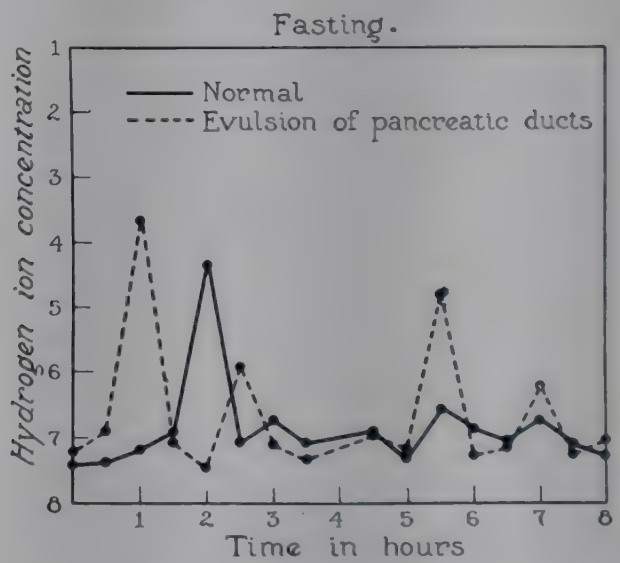


FIG. 59. Variation in pH of the duodenal content of the fasting dog before and after evulsion of the pancreatic ducts. (Courtesy, Hoerner: *Am. J. Digest. Dis. & Nutrition*, **2**: 294, 1935–36.)

from one to three hours after ingestion of food, i.e., when its buffering capacity is at a maximum, is capable of neutralizing an equal quantity of 0.1 N HCl. The bicarbonate concentration of pancreatic juice increases as the rate of secretion increases regardless of what the stimulus for secretion happens to be. The maximal concentration of bicarbonate in dog pancreatic juice is about 0.150 N, or about the same as the maximal HCl concentration of gastric juice (147).

Further studies reported by Hoerner (168, 169, 170) deal with the reaction of the duodenal content after pancreatic exclusion. The production of a pancreatic fistula did not alter the fasting pH range of the duodenal contents, although low determinations were more frequently obtained but the reaction remained at a lower pH longer when acid-stimulating meals were fed. Almost identical findings were obtained after evulsion of the pancreatic ducts (Figs. 59, 60).

It thus appears that exclusion of pancreatic secretions from the intestine impairs the acid-neutralizing mechanism to a greater extent than does the loss of bile. The significance of this factor for the etiology of peptic ulcer is clouded by the disagreement in the literature regarding the incidence of ulcer following loss of the pancreatic juice. If we follow Elman, and Matthews and Dragstedt (175), we can conclude that ulcer is frequent and that it is due to loss of the principal neutralizing component in the upper intestine. If we accept the findings of Berg, we must adopt the opposite stand. On the basis of our own observations, ulcers may occur following complete diversion of pancreatic secretion, but they are not due

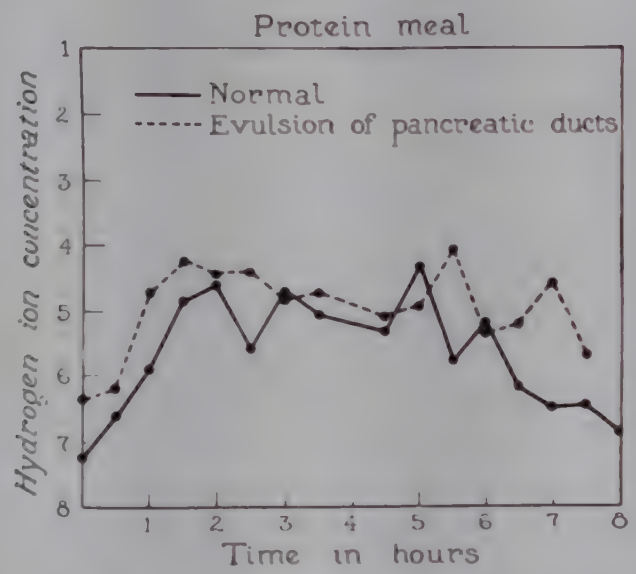


FIG. 60. Variation in pH of the duodenal content following a protein meal before and after evulsion of the pancreatic ducts. (Courtesy, Hoerner: *Am. J. Digest. Dis. & Nutrition*, **2**: 298, 1935–36.)

primarily to an impairment of neutralization; because in our considerable experience with dogs surviving months or years after pancreatectomy, pancreatic duct ligation, and separation of the pancreas from the duodenum, we have rarely seen an ulcer in these animals. This is consistent with the experience of others.

Animals with a pancreatic fistula, losing juice to the outside, develop an acidosis due to the loss of alkali. Animals with the pancreatic juice excluded develop a postprandial alkalosis because they secrete acid gastric juice but cannot secrete an equivalent amount of base in the pancreatic juice. Both develop a fatty liver and both are devoid of the neutralizing and buffering action of the pancreatic juice. The chief obvious difference between the two, then, is that the fistula dog develops an acidosis which

might impair the neutralizing and buffering property of Brunner's secretion which would not occur in the dog with exclusion of pancreatic juice. Hence, we should expect duodenal ulcers to occur more frequently in the case of a fistula than in the case of exclusion. The amount of juice lost may be a factor in the divergent observations.

Therefore we recommend that the pancreatic fistula experiments be repeated, with studies of the acid-base balance, such as we (53) carried out in dogs receiving acid continuously (p. 218). We obtained evidence that acidosis renders the mucosa susceptible to the action of acid gastric juice; and it is possible that the success achieved by Matthews and Dragstedt in preventing ulcers in pancreatic fistula dogs by feeding large amounts of base may have been due more to combatting an acidosis than to neutralization. It would be important to study the effect of acidosis on the secretion of Brunner's glands.

Summary

Digestive Secretions

Sham-feeding, so designed that a reasonably large quantity of unbuffered gastric juice may come into contact with the stomach and duodenum for a period of from three to six hours each day, very rarely produces an ulcer of the gastric or duodenal mucosa.

Though the capacity of a 12-inch loop of duodenum to neutralize gastric juice (1800 cc. of 0.5 per cent HCl in 24 hours) is large, when 40 mg. of histamine dihydrochloride is placed in beeswax and injected intramuscularly daily in dogs (also other animals), ulcers of the duodenum and less frequently of the pyloric canal and pyloric antrum in the region of the lesser curvature are produced as a rule. Indeed, a duodenal ulcer has apparently been produced in human subjects by the daily injection of histamine.

The ulcer produced by histamine injection may theoretically be due solely to the corrosive action of gastric juice or to an angiotoxic action of histamine, or to a combination of both factors.

This question was studied by ascertaining the tolerance of the duodenal and gastric mucosa of the dog to the continuous infusion of acid solution into the stomach. It was found that from 1800 to 2400 cc. of 0.1 N HCl could be infused continuously day and night for 10 days without causing ulcer if acidosis was prevented by the administration of an equa amount of base intravenously. When the concentration of acid was increased to 0.15 N HCl (0.54 per cent acid, which closely approximate the maximum possible acidity of gastric juice), and given at the same rat as before, ulcers occurred in the majority of dogs within 10 days. Thi

rate and concentration of the infusion fluid represents the maximum volume and acidity the dog's stomach can produce in 24 hours in response to histamine stimulation. Therefore, the dog's stomach must secrete at or close to its maximum capacity before the tolerance of the duodenal and pyloric mucosa is overtaxed. This evidence does not prove that histamine may not exert some angiotoxic action. It does show that histamine may provoke ulcer solely by stimulating a maximal output of gastric juice for from 5 to 10 days.

It should be emphasized that this large quantity of acid did not slough out the duodenal or pyloric mucosa. It caused circumscribed ulcers. *This proves that a locus minoris resistentiae is involved in addition to excessive acid secretion. Logically the two factors cannot be separated.*

The exclusion of bile from the intestine results in the development of duodenal or gastric ulcer, chiefly the former, in a significant percentage of animals. The difference in the incidence of ulcer between an external (25 per cent) and an internal (36 per cent) biliary fistula is not significant. In both types of fistula the buffering action of bile and the bile salt are lost. The fact that these ulcers can be prevented by the oral administration of bile salts, as well as alkalies, gastric mucin, and vitamins A and D, shows that the loss of the buffering action of bile, and the slight loss of base from the body, is not so important as some nutritional defect due to the loss of bile. The incidence of ulcer in obstruction of the common bile duct (57 per cent) is significantly higher and shows that something is involved other than the loss of bile. Undoubtedly obstruction causes greater nutritional disturbances than the loss of bile rendering the cells more vulnerable to acid injury. Though the interdigestive secretion of gastric juice may be slightly increased, the pH of the duodenal contents appears not to be changed in the bile fistula or obstructed dog. Hence, existing evidence indicates that the development of ulcer in the bile fistula and obstructed dog is due primarily to a decrease in defensive mechanisms.

The exclusion of pancreatic secretion by fistula or separation from the duodenum, as might be anticipated, impairs the acid-neutralizing mechanisms to a greater extent than does the loss of bile. A slight increase in gastric secretion occurs and the duodenal contents tend to be more acid. However, unless the disturbance of digestion is treated by feeding raw pancreas or pancreatin (poor protein absorption) and unless the associated fatty liver is prevented by pancreas feeding, lecithin, choline, or lipocaic, a definite disturbance of nutrition occurs. This would decrease the defensive mechanisms. In the case of pancreatic fistula, the loss of base, unless compensated for by giving base, would produce an acidosis which might decrease the acid-neutralizing mechanisms of Brunner's glands and the duodenum. The discrepancies in the literature regarding

the incidence of duodenal ulcer in dogs having a pancreatic fistula or exclusion of pancreatic juice by separation of the pancreas are undoubtedly due to differences in the state of nutrition and acid-base balance of the dogs in the hands of the same and different investigators. Nevertheless, since the increase in gastric secretion is so slight in comparison to the normal tolerance of the mucosa to gastric juice, it would appear to be certain that the chief cause of the "pancreatic deficiency" ulcer is an impairment in the defensive mechanisms.

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OUTLINE OF CHAPTER 10

Experimental Production of Peptic Ulcer

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      1. Comment
   B. trauma to the abdominal wall
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      1. Comment
   D. infection
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IV. Summary

CHAPTER 10

Experimental Production of Peptic Ulcer

A great variety of procedures has been employed in an effort to produce peptic ulcers similar to those occurring in the human. We will attempt to present all of the available experimental literature according to the method or principle of approach to the problem. Some of the earlier experiments are included only as a matter of historic interest. Certain of the experimental methods for ulcer production fall under subjects which are presented in chapters which precede and succeed this one.

Local Factors Acting on the Stomach and Intestines

Introduction of Irritants into the Stomach

In 1869, Roth (1) produced erosions and ulcerations of the lesser curvature and posterior stomach wall in rabbits by introducing pills containing 0.3 Gm. of silver nitrate; he attributed the lesions to spasm resulting from the gastric irritation.

Decker (2) administered small quantities of hot fluids to two anesthetized dogs. One of the animals developed superficial ulcerations; to the author this served as an explanation of the occurrence of ulcers in cooks, who were constantly testing hot foods. This was confirmed in guinea pigs by Sternberg (3). We have found (59) that if water at 70° C. is introduced into the stomach of animals every day for a period of a week, autopsy usually reveals acute gastric lesions. In such instances, it is probable that in addition to the coagulation of protein in the cells, intense local contraction of the musculature in response to the irritant may occur, resulting in gastritis, hemorrhages, and hemorrhagic erosions. But it must be remembered that the direct introduction of hot fluids via a stomach tube is not strictly comparable to the tasting of small amounts of hot foods by chefs and cooks. We have observed (365) that if the dog's stomach is exposed to water at 70° to 75° C. for only one minute every week or ten days, an achylia results and the animals manifest severe malnutrition. The daily introduction of water at a temperature of 50° C. has no significant effect on the gastric mucosa. Some remarks on thermal injury to the gastric mucosa have already been made (p. 196).

Sternberg (3) observed gastric ulceration in guinea pigs by administration of 96 per cent alcohol, but Greggio (4) reported that no ulcers occurred in 26 rabbits receiving various amounts of Marsala wine or 16 per cent alcohol by stomach tube for periods up to 50 days. Friedenwald (5) administered alcohol to 120 rabbits in daily doses of 5 to 8 cc. for a period of from several months to over four years. Autopsies revealed chronic gastric ulcers in two cases and scars of healed ulcers in four others. To what extent the stomach tube may have been responsible for these lesions cannot be determined. In our laboratory, Wigodsky (60) gave dogs "cheap" bonded whiskey in amounts which would correspond to 1000 cc. daily for a 70 kilo man. In observations on 12 dogs for periods up to one year, no erosions or ulcers were noted. These dogs were kept on the stock diet throughout the experiment.

Layne and Carey (548) administered 75 cc. of 20 per cent ethyl alcohol daily by tube to four dogs for periods of 336, 394, 799, and 906 days respectively. Gastroscopic examinations revealed a generalized hyperemia of the gastric mucosa appearing within seven to nine days and becoming most prominent during the third to fifth weeks. Thereafter the hyperemia subsided gradually; after 200 days the mucosa showed no abnormality. No hemorrhages, erosions, or ulcerations were observed at autopsy. The relation of alcohol consumption to peptic ulcer clinically is discussed on p. 395.

Hanzlik (152) mentioned that gastric ulceration following the administration of salicylic acid was reported in 1876. The observation has been confirmed, and although more recent work indicates that systemic action may play a part, we are including this subject in the category of direct irritation because of the generally recognized epitheliolytic property of salicylates. Also, acetylsalicylic acid in the doses used in studies on dogs caused vomiting (153, 154), which in itself could account for the gastric lesions. It has been shown (155, 156) that in rats the subcutaneous as well as oral administration of aspirin caused a very high incidence of ulcers, proportional in severity to the strength of the dose. Interestingly enough, it was claimed that such ulcers were shallower and less frequent during May and June than during the period from September to April.

We (154) found that a single dose of 1 to 2 Gm. of acetylsalicylic acid caused an increased gastric acidity in dog and man, and in some instances a gastric retention. We did not work out the mechanism involved, but the evidence was clear that the augmented secretion was not due to local contact of the drug with the gastric mucosa. The rise in acidity and delay in evacuation were prevented when sodium bicarbonate was given simultaneously with the aspirin; this observation should be taken into account if aspirin is prescribed for an ulcer patient.

Caravati (549) stated that the oral or intravenous administration of salicylates in doses sufficient to produce symptoms of salicylism did not bring about any changes in the gastric mucosa as examined gastroscopically. He stated further, without giving any figures, that there was no increase in secretion and that no salicylate was excreted into the stomach.

Turck (6) stated that feeding mustard oil to a dog for as long as 14 months did not result in the production of ulcers. Suzuki (7) gave a dog suspensions of curry powder and paprika in very warm water, 5 per cent alcohol, and beer for five days; catarrhal and edematous changes developed in the pyloric mucosa.

COMMENT. A significant observation in humans raises the question whether experiments with irritants might not have been more successful had the proper type of irritant been used over a sufficiently long period. Bergsma (8) reported that peptic ulcer was common among the black people of Abyssinia, who subsist on a diet rich in red pepper. He writes:

> The chief articles of diet are a heavy sour bread and a sauce that is approximately 50 per cent cayenne pepper. The sour bread is in the form of an immense thin pancake; part of it is broken off, rolled up in the form of a cornucopia, plunged into the pepper sauce so that a few tablespoonfuls of the sauce fill the cone, taken into the mouth and, almost without mastication, washed down with copious drafts of honey-water. My first native meal of bread and pepper sauce caused numerous herpes blisters about the mouth, and I have since eaten it only occasionally and then diluted.
>
> When one considers that from the time native babies are weaned, approximately at the age of two years, until old age, the diet contains monotonously the same dishes of sour bread, pepper sauce, mildly intoxicating drinks and occasional beans, peas and slightly cooked or raw meat, it is not surprising to find disturbances of the stomach a common occurrence and, at an early age, a contracted and scarred pylorus.

Bergsma remarked that it would be of interest "to compare the incidence of gastric ulcer in other countries having a very high pepper diet with that of Abyssinia." McCarrison (9) and others have reported on the frequent occurrence of peptic ulcer in certain districts of India, particularly Madras and Travancore. A prominent feature of the diet in both these regions is red pepper. Dogra (354) describes the daily fare which is eaten by southern Indians from the age of two years onwards. Breakfast consists of rice cakes with pickles or raw onions; the midday meal features "kolambu," a gruel made by boiling tamarind, dhals, vegetables, salt, chillies, and condiments. However, the observers in India apparently do not consider the irritating character of the food to be as important in ulcer pathogenesis as the deficiency in proteins and vitamins, particularly A and B_2. Conversely, the ulcers observed by Bergsma may be as much a result of deficiency as of irritation.

It is not difficult to visualize a mechanism by which long-continued direct irritation of the gastric mucous membrane might lead to ulceration.

It is well known that the application of irritants to the gastrointestinal mucosa causes inflammation of the membrane and marked contraction of the muscularis. The inflammatory reaction imposes an added demand for blood to the part, while the muscle spasm impairs the blood flow; these conditions would culminate in necrosis if continued sufficiently long, or if repeated at frequent intervals. The process has not, as far as we are aware, been followed by microscopic studies, probably because the feeding of irritants to experimental animals has not been sufficiently prolonged to produce actual ulceration. In the light of Bergsma's observations, the time required for the development of ulcers by irritation from condiments is to be measured in years; although the native diet is eaten from the age of two years onward, ulcers apparently do not develop until adolescence at the earliest.

Trauma to the Abdominal Wall

Perhaps the first experimental inquiry into the relation of external trauma to gastric ulcer was that of Wittneben (10) in 1886. He anesthetized dogs one hour after the ingestion of two pounds of meat and struck the animals on the epigastrium with a hammer; this procedure was repeated four days later, after which the dogs were immediately sacrificed. In all three dogs studied, there were submucosal hemorrhages at the site of the most recent blow; the author considered that these might serve as the basis for digestion and ulceration of the mucosa, in spite of the fact that the original wound had healed completely. The same opinion was expressed by Ritter (11) after similar findings in two dogs, and by Van (12), who experimented with a large number of rabbits.

Gross (13) and Gibelli (14) criticised the foregoing experiments on the grounds that the trauma administered was too variable from one animal to the next. They met this shortcoming by standardizing the blow to the abdomen. In most of their experiments, bruises of the stomach were noted amongst a number of other intra-abdominal injuries. Healing was complete, or almost so, in animals sacrificed several days after the trauma.

Whether a single severe trauma to the epigastrium may cause peptic ulcer is an unsettled medico-legal problem. On the basis of the meager experimental evidence and of numerous cases reported clinically (cf. see Gray (15)), there is no reason to doubt that acute ulcer may result from external trauma. Ordinarily, such lesions, if not immediately fatal through perforation or hemorrhage, will heal rapidly and completely. If symptoms or a demonstrable lesion persist, there is a strong suspicion of a pre-existing ulcer. The mechanism of the traumatic ulcer is obvious. The sudden force acting on the epigastrium is transmitted to the wall of the stomach, causing a contusion; in addition, the stomach may be driven against the vertebral column. Ritter (11) considered the lesion to start as a hematoma in

submucosa, separating the mucosa from the underlying tissue and from its blood supply. The extent of the damage to the stomach depends in part on how much food it contains at the time of the trauma; for example, Vanni (12) found it difficult to produce mucosal damage by external trauma in fasting animals.

The effect of chronic trauma, such as the compression which occurs in cobblers leaning against the last, or in kyphoscoliosis, or in the wearing of constricting garments, has not, to our knowledge, been put to the experimental test. Such an investigation would be desirable in view of the possibility that the acute gastric ulcers formerly common in young women were due to tight lacing. (See Chapter 14.)

Exposure to X-rays

In the course of some experiments on the effects of x-rays on gastric secretion, we observed chronic ulcers of a Pavlov pouch (19) and of the duodenum and ileum (356) following irradiation; in fact, this seems to be the only method available by which one may obtain a gastric ulcer which persists for a considerable length of time after the responsible agent is withdrawn. Wolfer (16) employed this principle to produce chronic gastric ulcer in dogs by the following technique: The stomach is exposed, the anterior wall opened, the posterior wall everted through the opening and sutured to a lead plate with an opening 3 cm. in diameter. The area is then exposed to a prescribed dose of x-rays for 30 minutes; the lead plate is sufficiently large to protect the remaining gastric mucosa and abdominal viscera. After irradiation, the stomach and abdomen are closed. According to the author, every animal treated by this method developed chronic ulcer of the stomach; the exact length of time required for these lesions to appear and to heal was not determined, but in three dogs the ulcer was still present for a year or longer. A study of the effects of the ulcers thus produced indicated that the lesions did not cause hypersecretion or hyperacidity; when the ulcer was located two inches proximal to the pyloric sphincter, it had no effect on the emptying time of the stomach, but when it was located near the sphincter, the emptying time of the stomach was delayed.

Aue and Ceculin (17) made the above method more convenient by inserting radium needles under the serosa of the stomach. The 11 animals which survived the procedure were found to have chronic ulcers when sacrificed from 38 to 420 days after operation. Gastric analyses showed that after the production of these ulcers there was a temporary increase in gastric secretion, followed by a reduction below normal. The observation that the secretion was temporarily increased does not conform to our experience; we were unable to establish any doses of x-ray, large or small,

which would produce an immediate or a delayed increase in the amount or acidity of the interdigestive secretion or the response to a test-meal.

The susceptibility of the gastric mucosa to the action of x-rays is further indicated by the work of Engelstad (18); he irradiated 61 rabbits, some in the thoracic, and some in the gastric region. Autopsy revealed degeneration of the gastric mucosa in 42 of the rabbits; 25 of these had acute or subacute ulcers, eight of which had perforated, mostly on the lesser curvature.

COMMENT. X-rays produce necrosis of the epithelial tissues and change in the blood vessels. At first there is a delay in fibroblastic proliferation (20), and if the dose of irradiation has been too large, perforation may result. The fibroblasts are the first cells to recover from the effects of x-ray (20, 21); the proliferation of these cells leads to an overproduction of connective tissue, which results in an indurated ulcer that does not heal readily. The degree of overproduction will vary with the dose, since excessive fibrosis was not observed in the gastric mucosa when doses of x-ray just sufficient to depress gastric secretion were used (20).

After exposure of the acid producing area of the stomach to non-ulcer producing doses of x-rays, gastric secretion is usually temporarily reduced in dog (19) and man (22, 357). However, we did not recommend irradiation as a method of controlling gastric secretion for several reasons. First, our observations and those of Dawson (20) indicate that permanent injury may be inflicted on the gastric glands by a dose of x-rays sufficient to depress gastric secretion. Second, after the acute effects of smaller doses of x-rays disappear, the secretion of gastric juice in response to a meal usually returns approximately to normal. Third, tissues other than the gastric mucosa may be damaged by the x-rays. Perhaps we were over-cautious. Further consideration of this question will be found on page 9[illegible]

INFECTION

In 1888, Letulle (23) stated that the administration of cultures of staphylococcus pyogenes aureus orally or parenterally to guinea pigs resulted in gastric ulcers; similar results were obtained with dysentery organisms and with pyogenic streptococci. Such obviously acute lesions were thereafter produced by a number of authors using lactobacillus (24), diphtheria toxin (25, 26), pneumococcus (27), cocco-bacillus of Pfeiffer (28), blood from eclamptic women (29), and staphylococcus (30).

Following this early work, which was taken to indicate that infection might be an occasional or accessory cause of ulcer, attention came to be focussed successively on two main organisms as being of etiologic importance in ulcer formation; the first of these was the colon bacillus, the second a specific strain of streptococcus.

Colon Bacillus. In 1906, Turck (6, 31) claimed to have demonstrated that chronic ulcers could be produced in dogs by feeding broth cultures of B. coli daily for several months. Active cultures of organisms obtained from the feces of ulcer patients were said by the author to produce ulcers in 100 per cent of dogs; furthermore, the lesions occurred only when the organisms were given by mouth and not when injected intravenously. Photographs illustrating the ulcers comprise a museum of nonspecific changes in the stomach and duodenum (including Peyer's patches).

Bauer (32) and Gibelli (14) repeated Turck's experiments, with completely negative results; Steinharter (30) reported that the injection of an emulsion of B. coli into the ear vein of rabbits was followed within 24 hours by the formation of gastric or duodenal ulcers, but microscopic study showed that these were infarcts. In three dogs, Litthauer (52) injected highly virulent B. coli into the margins of excision ulcers; complete healing ensued without delay. Singer (33) stated that a high incidence of ulcers occurred in the fundic portion of the stomach of rats kept under poor hygienic conditions and fed a deficient diet contaminated with fecal matter and overgrown with molds.

Streptococcus. During a period of 10 years beginning in 1913, Rosenow (34–37) maintained that ulceration of the stomach could be produced regularly in laboratory animals by the intravenous injection of streptococci isolated from foci of infection in humans. Organisms from ulcer patients produced a much greater incidence of experimental lesions in rabbits, dogs, monkeys, guinea pigs, cats, and mice than those cultured from foci in other patients. It is interesting that streptococci isolated from the jejunal ulcers of Mann-Williamson dogs were shown to produce acute gastric and duodenal hemorrhages and ulcers in a high percentage of rabbits, with few or no lesions in other parts of the body. According to Rosenow, the streptococcus which produces gastric ulcers has a selective affinity for the gastric mucosa, where it produces local destruction of the glandular tissue, which is then digested by the acid gastric juice. An acute lesion thus produced may be made chronic by the constant discharge into the blood of the specific organisms lurking in distant foci. Production of ulcers by the injection of streptococci was also reported by Hardt (44) in dogs and by McCown (45) in a guinea pig.

A number of extensive investigations have been made of the elective localization of bacteria from peptic ulcer or from foci of infection in ulcer patients. The accompanying data taken from Haden (38), who confirmed Rosenow, show how widespread are the lesions following the injection of even "specific" streptococci (Table 11). Similar results were obtained by Nickel and Hufford (39); these authors then performed the following interesting experiment:

To determine still further the elective localizing power of these organisms, strains freshly isolated from rabbits with definite lesions of the stomach or duodenum were introduced into the pulp chambers of dogs' teeth in the hope of simulating a chronic dental focus in man. In some of the dogs, only the pulps of four teeth were infected: in others, gastroenterostomy was also performed. In both groups of dogs those that lived only several months manifested submucous hemorrhagic lesions about the gastroenteric stoma and distal loop of bowel, while in those that lived a year or longer definite chronic ulcerations tended to form on the lesser curvature of the stomach or in the distal loop of the bowel; in several, perforation occurred. At necropsy, a roentgenogram of the infected teeth frequently showed a rarefaction at the apex, and the majority of the cultures obtained from the pulp chambers, as long as one and two-thirds years after inoculation, contained the living streptococcus, which still maintained its ability to localize electively in the stomach and duodenum of rabbits when injected intravenously.

It is most unfortunate that these experiments on dogs, the most important phase of the authors' work, are unsupported by data or photographs. One must be skeptical of their recognition of ulcers because in their paper, figure 7, which is titled "Section through an ulcer of the duodenum of a rabbit," actually shows no more than a beginning erosion.

Table 11

LOCALIZATION OF BACTERIA FROM DENTAL INFECTION ON INTRAVENOUS INJECTION IN RABBITS (HADEN)

Group	*Number of Animals Injected*	*Number of Patients*	*Per Cent of Animals Showing Lesions in*							
			Joints	*Muscle*	*Kidney*	*Endocardium*	*Myocardium*	*Stomach and Duodenum*	*Brain*	*Eye*
1	535	191	57	27	38	18	11	7	7	23
2	45	12	36	27	22	9	18	53	4	11

Group 1—Animals inoculated from patients not known to have ulcer.
Group 2—Animals inoculated from patients suffering from ulcer.

Saunders (40) showed that the organism present in peptic ulcers from humans was an alpha-streptococcus; specific agglutinins for this organism were found in the serum of patients suffering from peptic ulcer, while control serum from individuals with other types of streptococcic infections contained much less agglutinin for this organism. The author believed that his findings proved the infectious etiology of peptic ulcer. However, Saunders was unable to produce ulcers in animals by injecting this specific organism, and he suggested that the reported production of hemorrhagic erosions and small ulcerations by large intravenous doses of various broth cultures of streptococci may have been the result of a foreign protein

anaphylactic shock type of reaction. Since laboratory animals are not subject to spontaneous gastric ulcers, Saunders suggested that they probably enjoy a normal resistance to the causative organism. Celler and Thalhimer (42) isolated a nonhemolytic streptococcus from human ulcers and injected cultures of this organism into rabbits; this resulted in superficial, noninflammatory lesions of the stomach, which the authors did not consider in any way analogous to human chronic ulcer. They were not convinced, therefore, that these organisms had anything to do with initiating the lesion or maintaining its chronicity. Pulvertaft (43) considered it unnecessary to postulate an elective localization of the streptococcus in order to explain the gastric lesions produced by Rosenow and others in rabbits, since in his experience such lesions could be produced by the injection of the streptococcal toxin entirely free of organisms. Bacteria found in the experimental lesions by previous authors could, according to Pulvertaft, have settled there as secondary invaders. However, in the experiments of Joranson and Simons (56), secondary infection was noted only in lesions in which the fixation of the tissue was delayed from eight to 12 hours after death.

Other Organisms. The causative organism of peptic ulcer was not a coccus at all, but a bacillus, according to Hoffmann (46). The author injected 5 cc. of stomach contents from a case of peptic ulcer into a guinea pig and produced gastric ulcers in that animal; from these lesions he recovered a gram-negative, fine, slender rod which he inoculated into another guinea pig and again produced the stomach lesions. The author named the causal organism "Bacillus Hoffmanni," but later tests showed that it was apparently not specific.

The concept of mycotic infections as a cause of peptic ulcer was stressed by Askanazy (47). According to this author, 30 per cent of guinea pigs inoculated with and fed a mixed culture from human ulcers developed chronic gastric ulcer; the incidence was much higher when pure cultures of oidium albicans were used, showing that the latter organism is of prime significance. This view could not be sustained by the experiments of Nicolaysen (48), Kirch and Stahnke (49), or Leinati (50). Merke (51) was unable to produce ulcers experimentally with oidium albicans but considered that this did not disprove the etiologic role of the organism in man.

Attempts have been made to induce chronicity in artificial acute defects of the gastric mucosa by infecting such lesions with B. coli (32, 52), staphylococcus (53), streptococcus (41, 42, 57), and other bacteria (55), without success.

Joranson and Simons (56) inoculated cultures of E. histolytica into the pyloric submucosa in 51 dogs and eight cats. Lesions ranging from hemor-

rhagic exudation into the submucosa to deep gastric ulcers were observed in 70 per cent of the animals. In the remainder, either the volume of material injected was too small to cause sufficient undermining of the mucosa to produce necrosis, or the resistance of the tissues to the lytic action of the ameba was high. It is not possible to determine which of these factors may have been operating; the amount of inoculum varied from 0.2 to 4.5 cc., but the authors did not make any observations relating the volume of inoculum to the occurrence of the ulcers nor did they perform control experiments using a fluid containing the same "flora of yeasts and bacteria" but without amebae. Apparently the healing of some of the lesions was delayed as compared with the rate of healing of excision ulcers, or ulcers produced by submucosal injection of corrosive agents. However, none of the lesions seem to have gone on to true chronicity. Nor is it justified, from the evidence in this report, to suggest the possibility of a causative relationship between *E. histolytica* and gastric ulcer in man. For instance, the authors, in pointing out the resemblance of the amebic lesion to human gastric ulcer, enumerate the following characteristics common to both: (1) localization of the lesion to the stomach, (2) predominance of single lesions, (3) tendency to extend through all layers of the gastric wall, and (4) marked tendency toward recurrence. But it is to be noted that (1) the stomach was deliberately selected as the site of inoculation, (2) the inoculum was introduced at a single point, (3) apparently none of the ulcers perforated, and (4) the "recurrent lesions" were not ulcers.

The contribution of Pasqualino (58) deserves only passing mention: he considered that peptic ulcer was an infectious process secondary to peritoneal inflammation. Experimental support for this concept was derived from the occurrence of pyloric ulceration in four of 16 dogs in which the author had injected a few drops of a broth culture of B. coli into the prepyloric fat.

Comment. It has been abundantly demonstrated that streptococci can be isolated from most ulcers of the stomach and duodenum, and that the intravenous injection of such organisms causes acute lesions of the mucosa. The mechanism by which these organisms operate to produce the lesion is a moot point. They may operate by "specific elective affinity," by serving as emboli, or by causing gastric or duodenal spasms which cause petechial hemorrhages that become secondarily infected. Our observations support the latter view; however, this is not entirely incompatible with the concept of "elective affinity," since one organism may produce more of the spasm-exciting substance than another, and the degree of spasm may vary from animal to animal.

We (61) have prepared dogs with a pouch of the pyloric antrum and have injected streptococci isolated from two human gastric ulcers by the

Rosenow technique and virulent streptococci from a case of osteomyelitis. These cultures were injected into the epiploic arteries of the pouch in five dogs, and submucosally in five others. Only local areas of edema and congestion which disappeared within three days resulted. Virulent streptococci, which on intraperitoneal injection killed dogs in 18 hours, when injected submucosally in the pouch caused a marked congestion and edema which disappeared in four days, and when injected subcutaneously produced a huge abscess.

Since we did not find it possible to produce ulcer by direct infection of the gastric mucosa of dogs with organisms isolated from human gastric ulcer by Rosenow's technique or by virulent organisms from other sources with all other possible factors controlled, we can only conclude that if chronic ulcer of the stomach is due to infection, either the dog has a high natural immunity, which we doubt, or a highly specific organism is required, or other essential factors must be associated with the infection. It is possible that an infection of the tissues about an acute ulcer may cause production of connective tissue or inhibition of proliferation of mucosal cells, which, *in the presence of other factors conducive to chronicity*, will result in a chronic ulcer.

We stress the importance of additional chronicity factors because of our observations (61) on the effect of feeding bacteria to dogs in which an experimental abrasion of the pyloric and duodenal mucous membrane had been made. Ten tubes of a culture of streptococcus 24 hours old were given daily by the stomach tube at a time when the stomach was empty. In five healthy dogs, the lesions healed without delay; this confirmed the observations of Wilensky and Geist (57). A sixth dog developed distemper after the operation and had recovered three weeks later. When this dog was sacrificed six weeks after operation, a large hyperemic, edematous, inflamed ulcer about 2 cm. in diameter was found at the point of laceration. Streptococcus viridans was isolated from the deep tissues adjacent to the ulcer. The experiments were then continued on two other distemper dogs and in two cachectic dogs with ligated pancreatic ducts. Six weeks after the production of the acute lesion, autopsy of one of the distemper dogs revealed an ulcer with congested and edematous edges and a thickened base. This dog had been fed Streptococcus hemolyticus. In the second dog, sacrificed eight weeks after the operation and four weeks after recovery from the distemper, a healing ulcer was found at the site of abrasion. One of the cachectic ligated-pancreatic-duct dogs showed, at the site of a duodenal abrasion, an indurated ulcer. No free acid was found at any time during the attack of distemper or during marked cachexia in any of these animals. We concluded that in order for infection to play a role in the extension of a mucosal lesion, at least two other factors must be

contributory; namely, a general lowering of bodily resistance and a temporary hypoacidity or anacidity. According to our further observations, the absence of hydrochloric acid is not in itself the important factor; we were unable (54) to delay the healing of acute ulcers of pyloric pouches by massaging bacteria of proven virulence into the ulcers twice daily. There being no acid gastric juice, under these conditions, to destroy the bacteria, it is clear that the exposure of an acute lesion in the stomach of a healthy dog to direct infection does not delay healing. Whether a gastric ulcer would become infected in consequence of a generally lowered body resistance in the presence of normal acid secretion we do not know; it would be difficult to obtain the experimental conditions necessary to check this point, since almost any procedure which impairs the general health of the animal would affect the secretory functions. The question is of practical importance in relation to the cause of recurrences of peptic ulcer.

Why do ulcer symptoms frequently recur accompanying an upper respiratory infection? A lowered resistance is obviously present, but so far as we are aware, there is no evidence showing that the acidity is increased or depressed. If it could be shown that there is a temporary decrease in the gastric acidity in peptic ulcer patients during the infection which precedes or accompanies the recurrence, the implications would be twofold: (a) that the mucosa of the upper digestive tract is in an abnormal state, since a mucous membrane which is not manifesting its normal secretory activity must be abnormal and (b) that bacteria, which ordinarily could not survive in the stomach because of the acidity, could invade the damaged tissue. It would be desirable to measure the interdigestive secretion of peptic ulcer patients at regular, frequent intervals for an extended period to determine whether or to what extent systemic infections, or indeed any other disturbances, predispose to such local changes in the upper digestive tract as would make it possible for organisms to be concerned in the ulcerative process. The fact that persons with achlorhydria or achylia do not develop infections of the stomach in association with upper respiratory infections indicates that other factors must be concerned.

Regarding the initiation of an ulcer by infection *per se* in animals or humans, the only possibilities that we can entertain are those of follicular abscesses or septic emboli secondary to a hematogenous infection. The resulting erosion may conceivably extend circumferentially and downward to form an ulcer, but again, all the evidence indicates that in the human other factors besides the presence of bacteria must be concerned since in the healthy animal such lesions heal rapidly.

Interference with Pyloric and Duodenal Function

Pyloric Obstruction. The development of gastric ulcer following experimental obstruction of the pylorus was apparently first reported by Talma (557) in 1890. He ligated the duodenum just distal to the pyloric sphincter in rabbits and dogs and described lesions in the stomach ranging from focal hemorrhages through free perforations. Talma noted that lesions invariably developed in the rabbits, which cannot vomit, but not consistently in dogs, which vomited constantly. He interpreted this as indicating that the factor of distention was most important in the development of the gastric lesions. In further support of this view, he observed that when 0.4 per cent HCl was placed in the stomach, without distention, the lesions were limited to the mucosa, and the hemorrhagic stage was absent. However, Talma's experiments were not sufficiently well controlled and were in most instances of insufficient duration. Lichtenbelt (62) tied a ligature around the pyloric sphincter in six rabbits and sacrificed the animals in from three to 12 days. He observed ulcerations, apparently erosions, mainly in the antral portion of the stomach. Since these lesions developed regardless of whether the rabbits were on a mixed diet or a milk diet, Lichtenbelt concluded that neither mechanical irritation from retained food nor the degree of acidity were the important factors. He attributed the ulcerations to impairment of the blood supply to the mucosa through spasm of the muscularis mucosae.

Latzel (63) performed extensive experiments investigating the effect of partial or complete obstruction of the pylorus in mice, rats, guinea pigs, and rabbits. The author states that he was careful, in placing the constricting ligature around the outlet of the stomach, not to interfere with the principal blood supply. Of 35 mice and rats with ligated pylorus, there were one or more ulcerations in 28, diffuse gastromalacia in two, a perforated ulcer in one, and marked distention without significant findings in four; all of these animals died, usually on the second day after operation. Ulcers occurred in three guinea pigs, one of which had a complete, and two an incomplete obstruction; these animals were observed from two to five days. Of four rabbits with complete obstruction, apparently observed from two to three days, one was negative and three had ulcers, two of which perforated. Latzel stated that in these experiments on ligation at or near the pylorus, ulceration tended to develop in the fundic portion of the stomach. In further experiments on six rabbits and six guinea pigs, a kink was produced in the outlet of the stomach by stitching the first part of the duodenum to the greater curvature of the stomach. Ulceration occurred in one rabbit and two guinea pigs; the

observation period was not recorded, but the author stated that the lesion were in the pyloric portion of the stomach. Unhappily, there were no gros or microscopic illustrations of any of the lesions reported, nor were ther any data on the acidity of the retained secretions.

Baggio (65) claimed to have obtained gastric ulcers in a number o

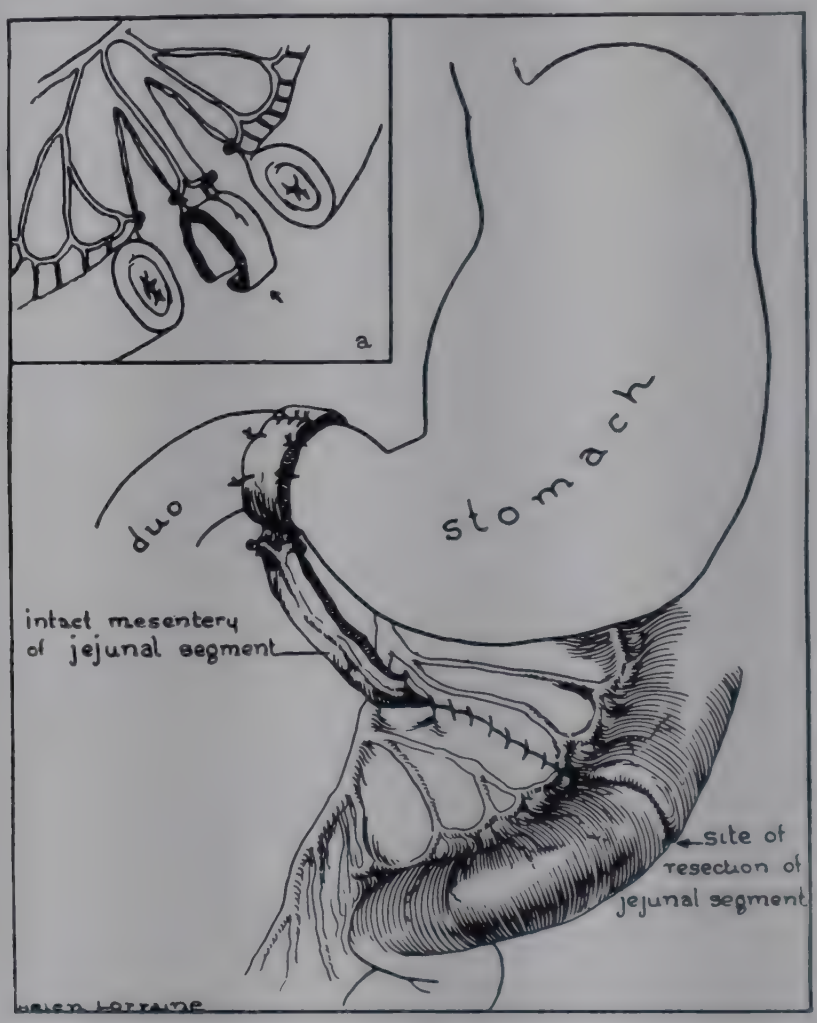


FIG. 61. Diagram of operation for placing around the pyloric ring a segment of jejunal muscle with intact mesentery. *a*, method of preparing the segment of jejunum by resection, antimesenteric section, and excision of the mucosa. (Courtesy, Morton: *Arch. Surg.*, **28:** 467, 1934.)

dogs in which partial pyloric obstruction was produced by suturing th anterior wall of the stomach so as to narrow the outlet.

An interesting method for producing pyloric dysfunction was devise by Morton (66), who placed a ring of jejunum around the pyloric sphinc ter. Seven dogs with this operation (Fig. 61) were observed from thre months to two years; x-ray studies during this time showed that th emptying of the stomach was less regular than in controls; the appearanc

was similar to that in patients with pylorospasm and other similar pyloric dysfunctions. The autopsies revealed some duodenitis, but no ulcers.

Recently, Shay et al. (67) have confirmed Latzel's (63) observations on the high incidence of gastric ulceration in rats and guinea pigs following ligation of the pylorus. In addition, they showed that the development of these lesions depends on the presence within the stomach of a sufficient volume of normal gastric juice for a sufficient length of time. They explained the importance of the volume factor on the grounds that the rumen of the rat's stomach is not exposed to the gastric secretion when present in small amounts, due to a limiting ridge between the rumen and the corpus. Evidently the authors do not share Latzel's belief that stretching of the wall of the rumen, with resulting ischemia, is important in the genesis of the lesions. However, it is not clear from their experiments that the relative significance of this factor has been evaluated. Since time and volume, particularly the latter, were found to be the critical factors, it would appear desirable to delineate more clearly in further experiments to what extent the volume exerts its effect by bringing acid into contact with the rumen as compared with distention of the wall.

The lesions described by Shay et al. (67) exhibited primarily an intense inflammatory reaction, characterized by swarms of polymorphonuclear cells, quite unlike the onset of the acute peptic lesion as described in Chapter 8. As the authors remarked, and as is well illustrated in their figures, the inflammatory aspects are more impressive than the ulcerative. Moreover, they state: "No ulceration was seen to involve more than the thickness of the epithelial layer—the base being invariably the tiny abscess overlying a still intact layer one or two epithelial cells in thickness. . . . The pouting described gives the impression that the initial damage in the glandular part of the stomach may occur in the crypts rather than to the surface cells." In the light of these statements, it may be that the primary necrosis is not due to the digestive action of acid and pepsin.

Harkins and Hooker (550) reported that vagotomy affords complete protection against ulceration in the Shay rat. The average volume of gastric content in the controls was 14 cc. as compared with 7 cc. in the vagotomized rats; the free acidity was 17 and 7 units respectively.

We (552) have observed the development of acute erosions of the gastric mucosa, especially the fundic region, in dogs under nembutal anesthesia with the esophagus and the pylorus ligated and histamine being administered every half hour when the intragastric pressure was maintained at a level of 35 cm. of saline. These lesions develop within a few hours.

Effect of Pyloric Obstruction on the Healing of Mucosal Defects. Bolton (68) produced an artificial pyloric stenosis in cats by

tying a band of rubber tubing around the duodenum just distal to the pylorus. Subsequently, he made ulcers in the stomachs of these animals by injecting gastrotoxic serum submucosally. He found that healing of these lesions was delayed to twice the normal time in the presence of any considerable degree of obstruction. Bolton considered that the basic cause of delayed healing in these experiments was an interference with normal granulation of the base of the lesion, due mainly to retention of gastric juice, and in some instances possibly to secondary bacterial infection. However, he did not make any studies to determine whether organisms were actually present, and, if the degree of acidity was appreciable, it is unlikely that bacterial activity was a factor in delaying the healing of the acute lesions.

Friedman and Hamburger (64) made similar observations in dogs; in their experiments, the acute gastric ulcers were produced by the submucosal injection of silver nitrate. In control animals, these lesions healed in two or three weeks, while in the operated group there were all stages from simple delay in healing to chronicity. The authors concluded that three factors are necessary for the production of chronic gastric ulcer in animals, viz.: (1) local destruction of the mucosa, (2) active or overactive gastric juice, and (3) hyperperistalsis, which causes a prolonged and vigorous contact of the acid with the acute lesion. Therefore, in human ulcer the cardinal factors are (1) abrasion of the mucosa by food particles and (2) reflex pylorospasm. This view was supported by the experiments of Hughson (69), who attempted to produce pyloric stenosis by sectioning and immediately suturing the circular fibers of the pyloric sphincter; he found that the emptying time was shortened rather than delayed by this maneuver, and that acute lesions made by excision of the gastric mucosa healed twice as rapidly in these dogs as in those with intact pyloric sphincters. Thus, the author was able to demonstrate a relationship between the emptying time and the duration of ulcer of the stomach. This was in contrast to the previous findings of Stuber (70), who conceived the idea that a pyloric insufficiency might be the cause of ulcer by the digestive action of trypsin regurgitated into the stomach. The experimental conditions necessary to investigate this hypothesis were obtained in dogs by removing a rectangular piece of muscularis from the anterior wall of the pyloric antrum and duodenum; the dogs were then fed a diet designed to stimulate the secretion of trypsin and at the same time depress the gastric acidity (milk, sodium bicarbonate, water, bread, and potatoes). Of five test animals on this diet, three developed pyloric ulcers and two had erosions; in two dogs with ligated pancreatic ducts, no ulceration occurred. Furthermore, ulcerative lesions were produced in one dog by feeding one half teaspoonful of a trypsin solution and 10 cc. of 0.1

NaOH. The author concluded from these results that ulcers of the upper gastrointestinal tract were "tryptic" rather than "peptic." Neither Greggio (4) nor Katayama (71) could confirm these experiments.

Other Gastric Motor Disturbances. The reportedly high incidence of gastric ulcer in conjunction with epigastric hernia prompted us (72) to investigate the possibility of a causal relationship between the hernia and the ulcer. Epigastric hernias were produced successfully in 13 dogs in such a manner as to exert a tugging action on the greater curvature of the stomach along the pyloric antrum. Since no ulcers occurred in any of these animals in an observation period extending up to six months, we concluded that the concomitant occurrence of epigastric hernia and gastric ulcer in man is a coincidence.

Lotzin and Kilchherr (73) undermined the mucosa on the anterior and posterior walls of the stomach and sprinkled diatomaceous earth between the layers in order to bind them together by an irritative reaction. The authors wished to see whether this interference with the normal free movement of the mucosa over the muscularis could result in gastric ulceration. The first dog, sacrificed at four weeks, was negative; in each of two dogs autopsied at three months, there was a solitary ulcer of the greater curvature, which had healed in one of the dogs; a fourth dog, examined six months after operation, had a scar near the greater curvature.

Duodenal Stasis. Stagnation of the duodenal contents has been proposed as a possible contributory cause of peptic ulcer. Sweet and associates (74) sectioned the duodenum 10 to 30 cm. distal to the pylorus, closed the cut ends, and performed a gastrojejunostomy; erosions, but no ulcers, occurred in the blind tube of duodenum. Other methods of obstructing the duodenum also yielded negative results. Slocumb (75) produced duodenal obstruction in dogs by two methods: (1) the duodenum was doubled upon itself and sutured in such a way as to present a flattened S-shaped curve, with a resulting partial obstruction amounting to 75 per cent or more; (2) infolding tucks were taken in the long axis of the bowel. The latter operation was much less efficient than the former. Sixteen dogs subjected to these procedures were autopsied from four to 145 days postoperatively; in 12 there was definite ulceration of the duodenum, and in two there were healing ulcers. The writer concluded that stagnation of the gastroduodenal fluids plays an important part in the etiology of gastroduodenal ulcer. The findings of Slocumb could not be confirmed by Figurelli (76), who observed 10 dogs, or by Bert (77), who studied 16 dogs.

Comment. There is no doubt that ulcerative lesions of the stomach occur in rats, guinea pigs, and rabbits following ligation of the pylorus. Because of the rapidity with which these ulcerations develop, and because

of their peculiar microscopic characteristics, the relationship of these lesions to other types of experimental peptic ulcer and to that occurring in humans is unsettled. Latzel considered that the ulcerations produced by this method were analogous to those occurring clinically in the obstructed, dilated intestine, but Shay apparently does not embrace such a view.

In the dog's stomach, which functions more nearly like that of the human than does the stomach of a rat, ulcers have not developed following partial pyloric obstruction; on the contrary, an ulcer artificially produced in a partially obstructed stomach usually heals completely, although its healing is delayed to approximately twice the normal time. It is true that in most of the experiments on dogs the gastric retention was not as complete as in the rats, guinea pigs, and rabbits; however, we (78) did not observe any gastric ulcers in dogs even when the degree of obstruction was sufficient to cause increased gastric secretion and marked hypertrophy of the stomach. In one dog, after seven months of observation, the degree of stenosis was increased by a second operation; the dog died four days later, and autopsy revealed a perforated duodenal ulcer and no gastric lesions.

The increased length of time required for complete healing of acute gastric defects in the presence of retention was attributed by Friedman and Hamburger to hypersecretion and hyperperistalsis; Bolton believed that local invasion of the ulcer by bacteria was to be considered in some instances. In our experience, there is evidence that all of these factors must be taken into account, and in addition, loss of weight and disturbed nutrition were observed in some of our animals. In dogs which did not lose weight rapidly, the acute ulcers healed in normal time. We found (78) that during the immediate postoperative period following the experimental production of pyloric stenosis in dogs,* there is a decrease in gastric secretion, superseded by a definite increase above the control values. It is during the period of depressed secretion that infection of an acute ulcer might be expected to occur, if it is a factor in delaying healing.

We assumed that the hypersecretion observed in our dogs was due primarily to the prolonged action of food retained in the stomach. The experiments of Matthews and Dragstedt (79) showed that healing of artificial ulcers was delayed when a valve was placed in the pylorus in such a manner as to prevent regurgitation of bile and pancreatic juice into the stomach (Fig. 62). The authors found that the acidity was higher and longer sustained after the operation than before. However, it is to be noted that in their dogs the element of retention was also present, inasmuch as they noted that for two weeks after the introduction of the valve

* A report (80) on the same subject appearing 12 years later in an Italian journal under "original contributions" proves to be a verbatim reproduction of our paper.

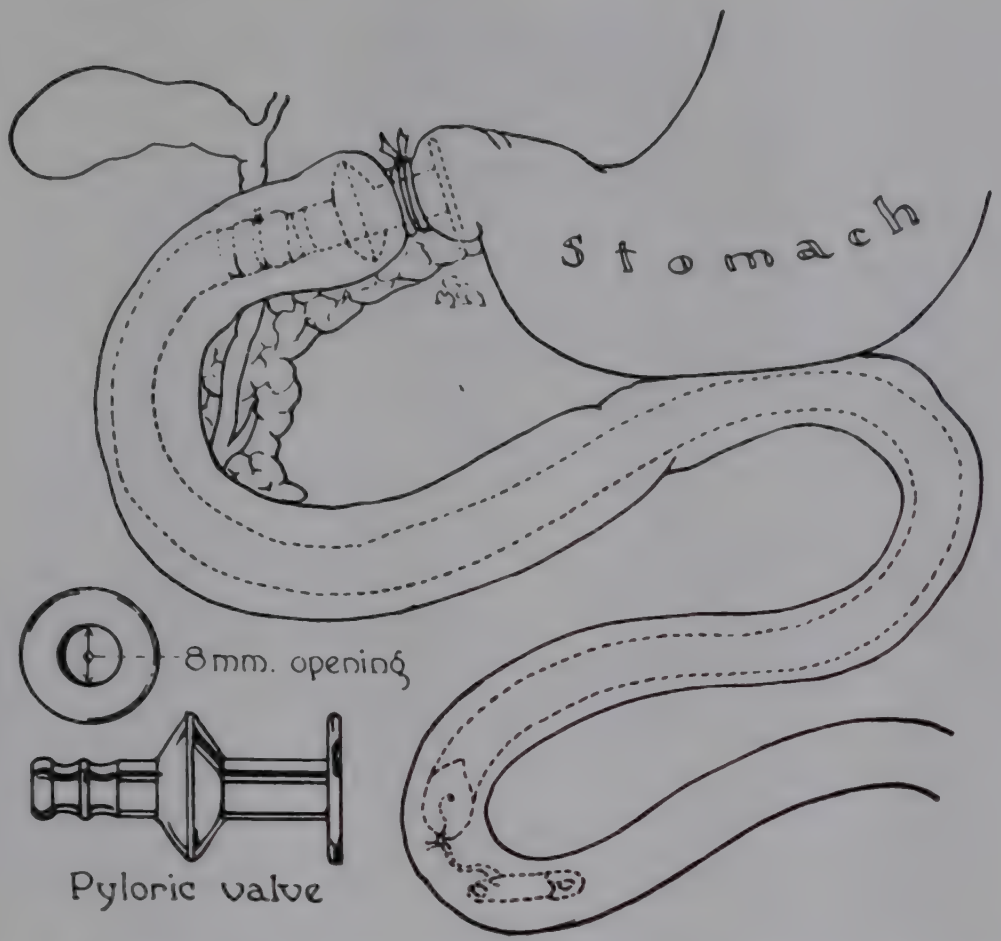


FIG. 62. Diagram illustrating the use of the valve to prevent regurgitation of duodenal juices into the stomach. (Courtesy, Matthews and Dragstedt: *Surg., Gynec. & Obst.*, **55**: 265, 1932.)

the emptying time was prolonged to 12 hours or more and that gastric peristalsis was more vigorous than before the operation.

The foregoing experiments provide an arresting illustration of the remarkable healing potential of gastric ulcer, showing, as they do, that these lesions almost invariably heal completely in spite of malnutrition, hyperperistalsis, and hypersecretion, and conditions which, temporarily at least, favor the growth of bacteria in tissue about the lesion. This is quite significant in view of the fact that patients with duodenal ulcer may have marked retention of highly acid gastric contents without developing gastric ulcer.

CIRCULATORY DISTURBANCE

Virchow (81) and Pavy (82) called attention to the importance of the blood supply to the stomach in protecting the mucosa from digestion by the gastric juice. They, as well as Cohn (83), attributed this protection to the alkalinity of the blood. Much of the experimental work done in an effort to demonstrate the role of circulatory disturbances in the etiology of peptic ulcer was based on the assumption that any damage to the

gastric mucosa was significant, because it was presupposed that the presence of acid gastric juice constituted a barrier to the healing of acute lesions.

We do not consider that an exhaustive review of the experimental contributions to this aspect of the problem would be of sufficient value to justify the space it would require; moreover, both Hauser (360) and Redwitz and Fuss (361) have covered the subject admirably. Indeed, such a review would be almost impossible because of the experimental design followed by many of the earlier investigators. In some reports dealing with a total of perhaps 20 or 30 animals, as many as 15 or 16 different attacks on the gastric circulation are described. Even in a single experiment in a single animal, multiple procedures are introduced. The following protocol (359) is quoted as an example of what may be encountered in the literature on the relation of circulatory disturbances to peptic ulcer:

Protocol 6.—Female dog, wt. 11 kilo.—Gastric content contains 7.1 per cent (SIC) free HCl and no blood.—20.I.1912. Laparotomy, adrenalin-injection—21.I. Dog receives mixed diet. Vomiting induced by subcutaneous injection of apomorphine every third day—24.I. Repetition of the adrenalin-injection in the stomach wall where a small induration of the first injection is found—30.I. Gastric content contains 6 per cent free HCl, no lactic acid and numerous red blood cells. 1.III. Dog killed. Gastric content contains 4 per cent free HCl, no lactic acid and numerous red blood cells. Examination of the stomach reveals nothing of note on the serous surface. On the mucosa, near the pylorus, corresponding to the site of injection, there are noted two small depressions, separated by ½ cm. The surrounding mucosa is drawn in stellate-fashion toward the ulcer margins. The ulcers have hard borders and are dark gray, the base partly covered with blood clots; on cross section these ulcers reach the muscularis. On microscopic examination one sees a granulation tissue which forms the base of the ulcer.

In view of the considerations mentioned, we will present this material in outline form for the most part, and discuss it in the light of more recent developments.

Ligation of Blood Vessels. Neither Mueller (362) in 1860 nor Roth (1) in 1869 were able to produce ulcers in rabbits by simple ligation of a considerable portion of the arterial supply to the anterior wall of the stomach. Their observations have been confirmed repeatedly (52, 61, 96, 107-111, 357) in all animals excepting the rat. For example, Litthauer (52) ligated three or four branches of the left gastric artery and vein on the lesser curvature near the pylorus in three dogs. At the same time, he excised a section of gastric mucosa in the area of impaired blood supply and cauterized the edges of this lesion with concentrated HCl. When the dogs were sacrificed one month later, healing was complete. This has been recently confirmed in dogs in which all the gastric vessels, either arteries or veins, were ligated (174).



FIG. 63. Injected and cleared normal specimen showing the blood supply of the rat's stomach. The three main branches arise from a common stem at *S*. The two fundic branches (*F*) and (*F*) are longer and wider than the single antral vessel (*A*). The fundus is more vascular than the antrum or rumen. (× 2.) (Courtesy, B. N. Berg: *Arch. Surg.*, **54:** 58, 1947.)

In rats, Berg (112) demonstrated that gastric ulcers could be produced in either the antrum or the fundus by ligation of the appropriate blood vessels. This phenomenon is due to the fact that in these animals there are no direct communications between the main gastric vessels. The central part of the antrum is supplied by a single artery; the fundus is supplied by an artery running on either side (Fig. 63). Ligation of the artery and vein to the antrum resulted in the development, within 24 hours, of a single punched-out antral ulcer in 10 out of 18 rats. Such

ulcers showed evidence of healing within eight days and advanced healing in 16 days. When the artery and vein were ligated to only one side of the fundus, ulceration occurred but once in 12 experiments, but after bilateral ligation of the fundic vessels, multiple ulcers were noted in most of the animals. Healing was more advanced in these lesions than in the antral ulcers, due to the more rapid establishment of a collateral circulation in the fundus.

Petrivalsky (358) is cited as having reported that partial occlusion of the superior mesenteric vessels resulted in, among other things, "true chronic ulcers in the duodenum."

Thrombosis and Embolism. Panum (84), in 1862, demonstrated that emboli produced by the intravenous injection of quicksilver resulted in lesions throughout the body, including the gastrointestinal tract; the necrotic areas in the stomach were considered potential sources of ulcer because of the action of the gastric juice. The author stated, however, that "although there remains, according to these findings, no doubt that a round ulcer may originate from an embolus, it does not follow that it must consistently and exclusively arise from emboli." Similarly, Cohnheim (85) injected a suspension of lead chromate into the gastric branches of the splenic artery in dogs; those examined on the following day had large, acute ulcers, while in dogs autopsied after three weeks the lesions had healed completely. Confirmation of these findings has been reported frequently, thrombosis of the vessels being produced by the injection of oil suspensions (86), formalin (86), charcoal (87), alcohol (88), lycopodium suspensions (89–91), and lead chromate (61), and by physical means such as freezing and heating (86, 87). Vigliani (92) did not observe ulcerations in rabbits and dogs in which the gastric arteries were thrombosed by injections of chloral hydrate.

In the opinion of Payr (86), Virchow's teachings on the effects of embolism tended to concentrate everyone's attention on occlusions in the arterial system and to overlook the importance of retrograde venous embolism and thrombosis. Payr reported changes in the stomach in rabbits, guinea pigs, cats, and dogs after producing thrombosis in the omental vessels by burning (hot salt solution) or freezing (ethyl chloride). He considered this as proof that emboli, breaking loose from thrombi in the gastric veins and passing in a retrograde direction into the submucosa and mucosa, were a likely cause of gastric ulcer. In support of this contention, he cited anatomic studies showing that in children the veins from the stomach contained effective valves which could prevent retrograde flow, and that these valves were, for the most part, no longer demonstrable after the age of 20. This he construed as one explanation of the rarity of ulcers in childhood. However, Payr's report presents no acceptable evi-

dence demonstrating a mechanism of the alleged retrograde embolism, and no convincing gross or microscopic illustrations of lesions resulting therefrom. The author declared that failure of previous investigators to produce gastric ulcers by ligation of the venous drainage of the stomach did not invalidate his findings, because ligation was less likely to result in much thrombosis.

Payr reported further that the injection of a suspension of lampblack or other particular matter into a mesenteric vein, together with portal obstruction, resulted in a reversal of blood flow and retrograde embolism, causing infarction in the area supplied by the vein. This was confirmed by Wilkie (87) but denied by Kobayashi (94), Yatsushiro (95), and Honda (89). The results obtained by Grossi (88) probably represent the true state of affairs; using Payr's methods, he could produce nothing more than acute lesions in dogs, and in all animals sacrificed after the third week, there were no gross abnormalities in the stomach.

Considerable experimental work was initiated by Eiselsberg's (125) observation that hematemesis not infrequently followed the removal of parts of the omentum. He considered that the most likely explanation was retrograde embolism from thrombi in the ligated veins. He found that removal of the omentum resulted in multiple hemorrhages of the gastric mucosa in rabbits, but not in rats. Similar experiments were performed by a number of investigators (87, 92, 120–123), all of whom reported at least occasional instances of punctate hemorrhages or erosions in rabbits, dogs, and guinea pigs. Engelhardt and Neck (121) suggested that the possibility of infection should be ruled out before these lesions could be ascribed to interference with the circulation, but Sthamer (122) stated that the ulcerations occurred when the omentum was removed with the strictest asepsis.

Omata (123) was able to produce "typical" peptic ulcers in rabbits by complete removal of the omentum with the vessels along the greater curvature of the stomach. These ulcers formed on the greater curvature 1 to 2 cm. proximal to the pyloric ring. Usually, they healed within one month and always within three months. However, according to a report of other Japanese investigators (124), this method was not productive of chronic ulcer unless the animal was previously inoculated with rabbit sarcoma.

Recently, Baronofsky et al. (93) reported that the intravenous injections of fat caused erosions or ulcers in cats, dogs, and guinea pigs, but not in rabbits. However, when intramuscular injections of histamine in beeswax were given to rabbits following the intravenous injection of fat, ulceration resulted in five of the six animals studied; with histamine alone, no ulcers were observed. These findings were interpreted as indicating

that fat emboli released into the blood stream, as for example in a fractu or operative manipulation of a bone, might occlude the end vessels i the gastric or duodenal mucosa, which then becomes less resistant to acid peptic digestion than normal mucosa.

Venous Stasis. Honda (89) published excellent gross and microscopi illustrations showing that the production of venous stasis delayed th healing of ulcers resulting from the injection of Lycopodium suspensio into a gastric artery; this was confirmed by Nakano (91). However, gastri venous stasis does not, in our experience (363), materially delay th healing of an excision ulcer of the stomach.

Nicolosi (102), investigating a supposed relationship between chroni splenomegaly and gastroduodenal ulcer, was unable to produce an lesions of the upper digestive tract by disturbing the arterial and venou circulation of the spleen in dogs and rabbits. According to Baronofsky an Wangensteen (103), gastric venostasis produced either by ligation of th splenic veins or obliteration of the portal vein "abets the ulcer diathesis." They observed that while interference with the venous return did not i itself cause ulcerative lesions of the stomach, it hastened the appearanc of such lesions in dogs injected with histamine. Also, in rabbits, whic ordinarily do not get ulcers following histamine, the ligation procedure i conjunction with histamine injections resulted in "ulcers and or erosions in almost 80 per cent of cases.

Vasomotor Disturbances. The development of digestive tract ulcera tions as a result of circulatory disturbances has been described in a experimental study by Penner and Bernheim (97). Investigation o clinical autopsy material had convinced the authors that certain peculia ulcerations of the gastrointestinal tract were the result of vasomoto changes known to occur in shock, and the experiments were undertake in an attempt to reproduce the clinical picture. Large doses of adrenalin injected intraperitoneally to prolong the vasoconstrictor action, wer administered to dogs, cats, guinea pigs, and rabbits. Lesions occurred i all parts of the digestive tract, varying from petechiae to large ulcerations Microscopically, it was found that the histogenesis of the lesions in th rabbit and guinea pig was similar to that in the human, in that th histologic changes first appeared in the submucosa, whereas in the do and cat the changes began in the mucosa. These differences were ex plained as being related to the location of the arteriovenous anastomos in the intestinal walls of the various species (see p. 190). In any case, th process consisted of prolonged vasoconstriction (clinically initiated b shock, experimentally by adrenalin), tissue anoxia, a drop in pressu gradient in the capillaries, increased capillary permeability resulting edema, diapedesis, and, finally, tissue necrosis with its sequelae.

Congestion, hemorrhage, and occasionally necrosis of the duodenal mucous membrane have been observed in shock produced by bleeding in experimental animals (98, 99). Furthermore, the production of a severe anemia by the injection of hemolytic agents (pyrogallic acid, pyridine, phenyl hydrazine), not in themselves sufficient to induce ulcer (113–115), has been reported to cause extension and even perforation of lesions produced by ligation of gastric arteries in dogs (116), excision of mucosa in rabbits (117), injection of dermatol into the veins (118), and bilateral vagotomy in dogs (119); the latter finding was not confirmed by Zironi (114, 115) in rabbits.

Closely allied to shock is the "alarm reaction" of Selye (100), in which gastrointestinal lesions, particularly in the stomach and duodenum, regularly occur. Selye attributes these lesions to the action of H-substance released by pharmacologic or physical trauma to the organism during the "alarm reaction." Experiments in albino rats (101) indicated that the gastric lesions which appear in the course of a severe alarm reaction (produced by high spinal cord transection, subcutaneous injection of formaldehyde, or exposure to cold) may be prevented by the prophylactic administration of various food substances, by aluminum hydroxide gel, and especially by comparatively small amounts of dextrose orally or parenterally. It is odd that the lesions were prevented by amphogel but not by sodium bicarbonate, especially since in the latter case the gastric contents were found to be neutral. Moreover, the authors' conclusion that glucose prevented the formation of these lesions "even in doses insufficient to raise the glucose content of the blood above the normal level" is not adequately supported by their data.

That hemorrhages and erosions of the gastric mucosa are a common sequel of severe systemic disturbances is amply attested by animal experiments. For example, Rehfuss (150) found gastric hemorrhages and ulceration in 85 per cent of guinea pigs injected with small doses of diluted scloderma venom. Investigating the nature of this phenomenon, he discovered that similar lesions could be produced by toxic doses of pilocarpine, atropine, paraldehyde, chloroform, 10 per cent phenol, saturated solution of magnesium chloride, sodium fluoride, copper sulfate—in fact, by almost any biologic material or chemical reagent given in toxic doses. These toxic ulcers were thought to be due to peptic digestion, because the author claims to have prevented them by feeding the guinea pigs 4 per cent sodium bicarbonate by stomach tube; he also expressed the belief that these acute lesions might become chronic if the animals survived long enough.

Numerous other experiments dealing with the appearance of gastric lesions in animals succumbing to the effects of toxic agents have been

reported. Those which have come to our attention are summarized in Table 12.

Table 12

TOXIC AGENTS WHICH HAVE BEEN REPORTED TO CAUSE GASTRIC LESIONS IN EXPERIMENTAL ANIMALS

Agent	*Animal*
Cantharides (146)	rabbit
Antimony Tartrate (147)	rabbit
Tetrahydro-B-naphthylamine (148)	guinea pig
Kallikrein (105)	rat
B-naphthol (104)	
Muscarine, Picrotoxin (160)	rat
Morphine (161, 364)	rabbit, cat
Atropine (166)	rabbit
Adrenalin (97, 164, 173)	dog, cat, guinea pig, rabbit
Eserine (166)	dog
Ergotine (167)	dog, guinea pig
Nicotine (168)	guinea pig
Sulfur Dioxide (in atmosphere) (149)	mouse, guinea pig

Vasomotor factors in peptic ulceration following burns, nervous disturbances, and endocrine disorders will be discussed under those respective headings.

LYMPHATICS. Ramond et al. (106) injected a suspension of animal black into the anterior wall of the stomach in dogs and rabbits and found that the lymphatic drainage was visible over the entire anterior and posterior walls, but disappeared near the pyloric antrum, and then reappeared in the two peritoneal leaves of the lesser omentum. Since these two leaves are not usually attached at their origin (as are those of the greater omentum), the result is that the right boundary of the stomach is devoid of lymphatics. The authors considered that this anomaly might explain the ulcer diathesis; the treatment, on the basis of their findings, would be to join the mesenteric leaves at the edge of the stomach.

COMMENT. The experimental evidence makes it clear that a considerable part of the stomach may be deprived of its blood supply in all animals except the rat without causing chronic peptic ulcer. On the contrary, a reduction of the blood supply to the stomach is a recent innovation in the *treatment* of the disease (367, 368).

Hauser (360) rightly stated that the negative results of ligation of the arterial supply to the stomach were of little significance; the results, he said, would probably have been different had the investigators tied off the

arterioles in the submucosa, for these are "functional end arteries." The difference would be, of course, that an acute focal lesion would result; however, this lesion heals rapidly, as indicated by Berg's work on rats and by the experiments in which the smaller arteries were occluded by the injection of particulate matter. The same effect is obtained by excision of a section of mucosa together with the underlying submucosa and part of the muscularis. Such a lesion also heals rapidly, even in the presence of an intense venous stasis such as we have produced by ligating all of the veins of the stomach.

It is obvious that a hemorrhagic or anemic infarct may occur in the stomach on the same basis that it occurs in other organs, and undoubtedly there are cases of gastric ulcer occurring in persons past middle age in whom the lesion originates in such a manner. These are probably the individuals who develop their ulcer late in life and in whom the lesion, once healed, does not tend to recur, at least not with the rhythmicity characteristic of most ulcers.

Hauser's exhaustive inquiry into this problem included classic studies on atherosclerosis, thrombosis, and aneurysmal dilations of the vessels in the wall of the stomach. At the time of his work, gastric ulcer was much more common than duodenal ulcer, and the disease affected predominantly the age groups in which arteriosclerosis was common. For example, Hauser's analysis of the literature on the incidence of peptic ulcer led him to conclude that the disease was essentially one involving individuals past the age of 40. Recent data on the age of onset of symptoms in gastric ulcer (555) confirm Hauser's figure, the highest incidence occurring in the fifth decade (p. 616). He rejected the clinical opinion that the development of the lesion occurred much earlier than was apparent in autopsy material, because he considered that the clinical diagnosis was generally based on the onset of symptoms and not on the demonstration of an ulcer. Thus, he concluded that "it cannot be disputed that a great number of ulcer cases are attributable to circulatory disturbances, a part of which are brought about by thrombosis or rupture of diseased vessels, and a part by embolic obstruction of the same." He ignored the peptic ulcers of young women and men below the age of 30 years. It is especially in the ulcers of later life that atherosclerotic vascular changes may play a role. In any case, the facts indicate that there is not the least justification for considering, as many recent authors do, that the so-called "vascular theory" is a rather obsolete point of view.

Boles (369) expresses essentially the same opinion. He and his associates (370) demonstrated that acute gastric lesions found at autopsy are usually only one manifestation of a generalized circulatory insufficiency brought about through quantitative, qualitative, or vasomotor alterations

in the circulatory system. These lesions are presumably not of the a
mucosal type described by Penner and Bernheim (371) as occurring s
quent to shock, because Boles et al. observed evidence of chronic cha
in the deeper layers in practically all cases.

But all studies of this kind are difficult to reconcile with certain cli
and experimental observations. Since there is hardly any doubt t
that peptic ulcer, or more specifically, duodenal ulcer, usually ha
onset before the age of 40, Hauser's correlation of the age of arterioscle
with the age of onset of peptic ulcer is untenable as far as duodenal
is concerned. Even in the modern work of Boles et al. (370), the age
relation is not clear. They state that their cases were chosen from
levels which would correspond with the incidence of clinical cas
ulcer. Their table shows that some 30 per cent of the autopsied indivi
were under 30 years of age; some 15 per cent were under the age o
They state further that the mucosal changes described were almost al
superimposed upon "chronically degenerated submucosal and musc
layers." Does this mean that the changes which the authors attribu
circulatory disturbances, which in turn are proposed to be a facto
chronic peptic ulcer, are equally common in children? If so, how can
be reconciled with the observed rarity of gastric ulcer in childh
Obviously, it must mean that the circulatory disturbance is at most
an underlying factor upon which some other factors, as yet unident
must be superimposed in order to produce a chronic ulcer. Thus cli
observations lead us to the same conclusion in regard to the vas
theory as did experimental studies.

Systemic Factors Acting on the Stomach and Intestine

Burns

Good reviews of the literature on the occurrence of peptic ulcer fol
ing burns (Curling's ulcer) have been contributed by Riehl (381) an
Harkins (130). The latter points out that Curling's (126) descriptio
this lesion in 1842 was preceded by several authors (127-129).

Welti (131), in 1889, noted that when rabbits' ears were immer
for several minutes in water at 57° C., lesions occurred in the stom
varying from hemorrhages to discrete ulcerations. The author consid
these changes due to thrombi liberated from the burned tissue. Busse
found duodenal ulcers in a 15 year old girl dying six days after a s
burn; to prove that these lesions were not a coincidence, he prod
extensive burns of the back in four anesthetized rabbits by immersi
boiling water. The three surviving animals were sacrificed four days

opsy showed marked inflammation and ulceration of the intestine, ecially the duodenum. Such observations have been confirmed re- tedly (133–135, 138, 141, 382). The best experimental study, and the closest approaching clinical observations, is that of Hartman (141). obtained distinct ulcers in 63 per cent of 50 dogs in which third degree ns of 50 to 60 per cent of the body surface were produced and dressings etrolatum or similar preparations applied. In a series of 30 dogs treated h tannic acid or other tanning agents, ulcer was present in 7 per cent.

ORIGIN OF EXPERIMENTAL ULCER FOLLOWING CUTANEOUS BURNS. *orption of Toxins.* Several investigators (133–135, 137, 138) have orted the development of erosions, hemorrhages, and areas of necrosis he stomach and intestine in animals following the injection of extracts nfusions of burned tissues. Robertson and Boyd (138) reported that transplantation of burned skin to a normal rabbit caused toxemia in some cases death, with congestion of the small bowel.

Release of Histamine. According to Harris (139), the histamine-like dilator substance present in normal skin disappears after scalding. t it is released into the circulation is suggested by the clinical and rimental literature reviewed by Behrmann et al. (383), as well as by r own evidence. They argued that the histamine did not, however, a role in the formation of the ulcer, because (1) the acidity was not eased in burned animals, and (2) penicillin-treated animals (384) did develop ulceration following burns despite blood histamine values l to those of untreated controls. Necheles and Olson (140) observed finite increase in the gastric secretion only in those dogs receiving venous saline concomitant with the burn. Recently, Friesen and gensteen (386) reported that if an animal receiving histamine is ected to a burn, ulceration develops earlier and is more severe than resulting from histamine alone; it was concluded that burns abet the diathesis.

Hemoconcentration. Experiments performed by Friesen and Wangensteen) on dogs subjected to 40 per cent third degree burns indicate a direct ionship between the occurrence of hemoconcentration and the de- oment of Curling's ulcer. Of five dogs receiving the burn, lesions of the oduodenal mucosa were present in the four animals which mani- d a hemoconcentration, and absent in the one dog which did not. 4 dogs receiving the burn plus histamine in beeswax, gastroduo- l changes were absent in only the two animals showing no hemocon- ration. An attempt was made to prevent the hemoconcentration in urned dogs (also receiving histamine) by the administration of plasma; hree animals in which the effort was successful developed no gastro- enal lesions.

Comment. It is apparent that only in recent years have any well-controlled experiments been directed at elucidating the mechanism of the Curling ulcer. Harkins (130) presented a list of the theories hitherto advanced; omitting, for purposes of serious consideration, those which are not theories but apparently gibberish (e.g. "the antiferments of the mucous cells are reflexly destroyed") and those which overlap, we have the following hypotheses to serve as a basis for investigation:

1. Compensatory Hypertrophy of Brunner's Glands. This hypothesis was advanced because the duodenal glands were observed to be hypertrophied in some cases of inflammation and ulceration following burns. It was presumed that the hypertrophy represented an effort at compensation for the loss of excretory function of the burned skin. For example, Socoloff (136) found ecchymoses and acute ulcerations of the stomach in animals which developed toxic manifestations after varnishing of the skin. Such experiments were performed because it had been accidentally observed that the gilding of children taking the part of cherubs in a religious celebration caused death.

The probability is that a hypertrophy of Brunner's glands would be secondary to the congestion in the duodenum, or at least a part of the whole process, and not a cause of it.

2. Excessive Gastric Acidity. The gastric secretion following burns has been studied especially by Necheles and Olson (140). They found an increased secretion in some of their dogs, but ulceration occurred in only one of the 16 animals. Furthermore, duodenitis was present in animals in which the pylorus had been ligated; therefore, the duodenal lesion could not be attributed solely to the action of gastric juice. The most striking disturbance in gastric function after burns was the intense increase in motility; the mechanism of this phenomenon was not worked out entirely. The increased motility was unaffected by section of the vagi or splanchnics but was abolished by atropine; Necheles and Olson raised the question whether the burn might cause an inhibition of choline esterase. In a later study, these investigators (366) showed that although atropine prevented the hypermotility, it did not prevent the increase in gastric secretion which sometimes occurs following burns.

3. Direct Action of Heat on the Intestine. This view is not tenable because gastroduodenal lesions occur following burns not involving the abdomen. For example, in Harkins' (130) collected cases, out of 52 in which the data permitted an analysis, the abdomen was not burned in 29.

4. Spinal Reflex from Burned Skin. This theory was advanced by Brown-Sequard (387) in 1858. He observed that no congestion of the viscera followed a burn of a hind limb of dogs if the sciatic and crural nerves were cut or if the lumbar cord was sectioned. Simonart (388) made

similar observations. The objection to these experiments in relation to Curling ulcer is that the latter often manifests itself after the period of shock following the burn has subsided. Indeed, a patient who appears well on the way to recovery from a severe burn may die suddenly of severe hemorrhage or of perforation of an ulcer two weeks or more after the accident.

5. Irritant Action of Noxious Bile. Hunter (389) proposed this theory in an effort to account for the localization of Curling's ulcer in the duodenum, whereas peptic ulcer was ordinarily found almost exclusively in the stomach. As proof that the elimination of toxins in the bile could produce duodenal ulcer, he cited his findings in dogs injected with a hemolytic drug, toluylendiamin. These animals developed congestion in the duodenum and not in the stomach, although no break of the mucosa was observed.

The alternate suggestion that the duodenal lesion results from a suppression of bile is not tenable because a considerable period of time is required for the development of duodenal ulcer following ligation of the common bile duct (see Chapter 9).

Nowadays, we are not so hard put to explain the localization of Curling's ulcer. It has been pointed out (Chapter 4) that, given conditions which tax the resistance of the mucous membrane of the upper digestive tract, the duodenum will succumb before the stomach. Thus, in Harkins' (130) collected cases, the duodenum alone was involved in 71 per cent, the stomach alone in 16 per cent. It would be of interest to observe the distribution of ulcerations following extensive burns in animals with gastroenterostomy.

6. Action of Burn Toxin. Whether toxic substances are vitally concerned in the genesis of Curling's ulcer has not been established. None of the toxic substances (142) alleged to be concerned have been identified.

7. Hemoconcentration. The occurrence of hemoconcentration following burns has been established (143, 144, 382), and according to Friesen and Wangensteen (382), the Curling ulcer is preventable if the hemoconcentration can be combated effectively.

8. Embolism. It has been shown (p. 282) that focal ulcerations in the stomach and duodenum may be produced by emboli. The supposition that the ulceration following burns is due to septic emboli from the burned area is therefore a perfectly good one, but by the same token the digestive tract lesions are only a part of the picture of focal infarction in all organs.

9. Adrenal Insufficiency. The occasional involvement of the adrenal glands in individuals dying with Curling's ulcer led to the suggestion that the ulcer may be due to adrenal damage. The subject of the relation of the adrenals to peptic ulcer is discussed in the section on endocrines

(p. 313). Suffice it to say that when an adrenal lesion occurs with Curling's ulcer, it is in all likelihood a resultant of the same disturbances which produce the gastrointestinal lesion.

10. Infection. Harkins (130) concluded from his survey that a burn is more likely to be complicated by gastroduodenal ulceration if sepsis develops. Experimental support for this view is provided by Hartman's (384) observation of a marked reduction in the incidence of Curling ulcer in dogs treated with penicillin after sustaining a burn. However, Hartman did not consider infection *per se* to be primarily concerned in the genesis of the ulcer, and we agree. It is more likely that the general lowering of resistance in patients with a systemic infection predisposes to progression of the acute ulcerative lesion which develops in the stomach or duodenum during the period before the burned area becomes infected. Gastric secretion under such conditions could lead to extension, perforation, or hemorrhage.

Of the foregoing theories relating to the development of gastroduodenal congestion, petechiae, hemorrhages, erosions, and ulcer following burns, the most tenable are those which have also been proposed to explain the phenomenon of shock, e.g., hemoconcentration, nervous reflex, absorption of toxins.* Therefore, we consider that the most logical explanation of the origin of Curling's ulcer is to be found in the congestion of the mucosa accompanying the state of shock which follows a severe burn (97, 145), rendering it susceptible to digestion by acid-pepsin.

Cinchophen

Production of Cinchophen Ulcer. During the course of some studies on the production of liver damage, Churchill and Van Wagoner (176) discovered that large doses of cinchophen given orally to dogs resulted in acute and chronic gastric ulcers in a high percentage of animals. Of 22 dogs receiving the drug in daily doses varying from 0.33 mg. per kilo to 27 times this amount, ulcers occurred in 17; 10 dogs had single ulcers on the lesser curvature near the pyloric ring, while the remaining seven had multiple lesions totaling 19 gastric and four duodenal ulcers. These findings, which have been confirmed repeatedly, made available a simple method of producing experimental chronic gastric ulcer.

In order to rule out the possibility that the ulcers obtained by cinchophen were due to direct irritation of the gastroduodenal mucosa, Churchill and Manshardt (177) introduced a suspension of cinchophen in olive oil into the intestine at a point four feet from the pyloric sphincter. In each of three dogs receiving 220 mg. per kilo per day by this route, autopsy after 10 to 22 days revealed typical peptic ulcers of the pyloric region.

* See Blalock (390) for a review of the factors concerned in shock.

Shoji (178) administered atophan (German trade name for cinchophen) to 60 rabbits and 50 dogs daily from one to 700 days; he found that dogs were very susceptible to the ulcerogenic action of the drug, whereas rabbits were resistant. This was confirmed by Schwartz and Simonds (179), who showed further that ulcers formed readily in cats receiving cinchophen, while guinea pigs succumbed to the toxic effects of the drug without developing ulcers. In chicks, cinchophen produces fewer and less severe lesions (180) than when it is fed in combination with diets deficient in the anti-gizzard erosion factor (p. 307) (181). The same dietary factors which are effective in the deficiency lesions are active against the cinchophen-induced lesions in chicks (182).

Extensive studies of the production of ulcers by cinchophen have been published by Stalker, Bollman, and Mann (184–187), working with a total of 131 dogs. The oral administration of 2 Gm. of cinchophen daily to 12 dogs on a regular diet was followed by the development of ulcers in 11 of the animals in an average of 18 days. To determine the effect of smaller doses over a long period of time, they fed 20 dogs 1 Gm. of the drug five days a week; ulcers developed in 19 dogs in an average of 270 days. It was shown further that the lesions could be produced by daily instillation of the drug into the jejunum or ileum, by rectal instillation, and by subcutaneous or intravenous administration of a neutral solution of the sodium salt of cinchophen. When the drug was administered orally to five dogs with fundic pouches where unbuffered acid is present, ulceration developed in the pouch in every case, while the main stomach remained relatively free from injury.

Nasio has carried out an intensive program of research on cinchophen ulcers at Rosario, Argentina, in recent years (206). He has demonstrated (188) that peptic ulcer may be produced consistently in dogs within a period of two weeks by the daily oral administration of 250 mg. per kilo in dogs weighing to 15 kilo, and of 200 mg. per kilo in heavier dogs. The drug was introduced by tube into the empty stomach. The dosage used by Nasio is somewhat higher than that customarily employed in producing cinchophen ulcer. For example, we generally give no more than 200 mg. per kilo per day, regardless of weight; also, we administer the material in capsules immediately after a meal in order to reduce the factor of local irritation.

It is obvious from this résumé that ulcers, especially of the stomach, may be produced regularly by the administration of cinchophen by any route in susceptible species.

Natural History of Cinchophen Ulcer. Bollman and associates (184) have discussed in detail the symptomatology and pathology of cinchophen ulcer. They say:

During the course of administration of cinchophen, certain signs and symptoms appear to be characteristic. During the first few days, the dogs appeared somewhat toxic, especially from one to six hours after administration of the drug. At these times they appeared stuporous but could be roused with little difficulty. If the animals refused food and administration of cinchophen was continued, the intoxication became more marked, but the incidence of formation of ulcer was definitely decreased. After a few days, the animal again appeared normal for a short period. Usually during the second week emesis, as a rule of mild degree, occurred, and at about the same time tarry diarrhea of variable but increasing severity was noted. An ulcer was not noted before tarry stools had been observed, and it was almost always noted after this symptom had appeared.

Some degree of anorexia and anemia usually was noted at this time, and often some loss of weight and decline in liveliness of the animals were noted. Death from perforation of the ulcer, or from hemorrhage, occurs more frequently during this stage of the procedure than during other stages, but in the absence of these complications the animals could be maintained for several months without much change in the appearance of the chronic ulcer. With the discontinuation of administration of cinchophen the animals rapidly returned to a normal-appearing condition.

Study of the stomachs removed from animals after varying periods of administration of cinchophen indicated the progression which occurs in the formation of this type of ulcer. Within the first few days the entire stomach appears somewhat edematous and hemorrhagic and the mucosa is more or less covered with small linear hemorrhagic erosions; usually along the lesser curvature appear several superficial, clean-appearing punched-out mucosal ulcerations which may be more than 1 cm. in diameter. They rarely extend deeper than the muscularis mucosae. About one week later the hemorrhagic character of the gastric lesions is less marked, but there are numerous clean superficial ulcerations of the fundic mucosa. In about another week the acute gastritis seems to have almost completely disappeared, and the number of acute ulcerations has greatly diminished. At this time a single, or at times a multiple ulceration of the pyloric region appears marked. Later the acutely ulcerated areas almost completely disappear and the typical-appearing chronic ulcer remains on the posterior wall near the lesser curvature in the pylorus. Often the ulcer may be seen from the serosal surface as a group of fine, white radiating lines of fibrosis passing outward from the reddish center of the base of the ulcer.

The healing of cinchophen ulcers was shown to be the same as that of other experimental, as well as human, ulcers. Nasio (188) confirmed these observations in every respect.

Simonds (189) re-examined the sections from the stomachs of dogs used by his associates (Van Wagoner, Churchill, etc.) in their original studies on cinchophen ulcer; he pointed out that the underlying lesion is a diffuse or focal gastritis which is evident within 24 hours after the first dose of the drug. Similar findings were reported by Hanke (171) in acute experiments, but his observations must be qualified to the extent that the preparation used by him contained sodium salicylate as well as cinchophen.

Factors Concerned in the Origin of Cinchophen Ulcer. *Liver Damage.* Attention is naturally drawn to the role of the liver damage (vacuolization and necrosis of the hepatic cells) which follows the administration

of cinchophen. Just what connection exists between impaired liver function and peptic ulcer is not yet known, but the experimental attack has been directed chiefly at the detoxifying mechanisms, particularly glucuronic acid conjugation. Miller, Brazda, and Elliott (190) attempted to exhaust the glucuronic acid reserve of the liver by feeding large amounts of borneol, which is excreted as borneol glucuronate; they showed that the administration of mucin prevented the drop in glucuronic acid excretion in fasting dogs receiving large doses of borneol. The authors did not pay particular attention to the possibility of producing ulcers by the continued administration of the drug. However, gastric ulcer was observed (380) in three out of 10 dogs receiving borneol in our laboratory.

Deloyers (192) contended that the intramuscular injection of proper doses of camphor in oil to dogs led to the formation of ulcer; he attributed this to a depletion of the glucuronic acid, which is an essential part of the molecule of mucin. In spite of this plausible explanation, the author's data on the production of ulcer by camphor is not convincing. However, we (193) were able to reduce the incidence of cinchophen ulcer in dogs from 100 per cent to 18 per cent by feeding 30 gm. of mucin twice daily; Stalker et al. (186) prevented ulcer formation in two of four cinchophen-fed dogs by the administration of mucin; and Winters et al. (194), using a 3 per cent pectin solution, observed a reduction in the incidence of cinchophen ulcers from 100 per cent in four control dogs to 11.1 per cent in nine treated dogs. In one dog examined repeatedly by gastroscopy and exploratory operation, Chiray et al. (218, 373) were able to observe repeated healing and recurrence of cinchophen ulcer following the administration and withdrawal of pectin. Pectin, besides being physically similar to mucin, resembles the latter chemically in its content of uronic acid.

Barbour and Fisk (195) observed equal degrees of histologic damage to the liver in dogs after the administration of cinchophen, tolysin, and sodium salicylate respectively, yet ulcers occurred only in the animals receiving cinchophen; however, as has been pointed out, ulcers may be produced by the administration of salicylates. Reymont (191) found that liver damage could be produced by cinchophen without the development of ulcer, and vice versa.

Ulcers have been reported to occur following impairment of liver function by ligation of a part of the portal return in rabbits (196), by partial hepatectomy (183), and by production of an Eck fistula (41, 183) in dogs. In the latter animals, the ulcers were reported to be prevented by elimination of rough food from the diet (183); the chronic inanition was corrected by feeding mucin or chondroitin, both of which contain glucuronic acid (197).

Effect on Gastric Function. Stalker and his co-workers (185) found that during the period of administration of cinchophen, the total volume of gastric juice secreted in response to histamine was increased twofold; they demonstrated further (186) that the incidence of cinchophen ulcer was significantly reduced by subjecting the dogs to various types of medical or surgical therapy aimed at the control of the acid. The authors concluded that the gastric acidity is an important factor in the experimental production of peptic ulcers by administration of cinchophen. Neuwelt and Necheles (198) were unable to confirm these findings in studies on four Heidenhain pouch dogs receiving cinchophen intravenously for as long as 39 days.* We (199) could not demonstrate a significant change in the secretory response to a test-meal in either Pavlov or Heidenhain pouch dogs after the daily administration of 100 mg. of cinchophen per kilogram of body weight, although five of the animals developed ulcers. However, Hey (367) stated that in nine dogs in which the arteries of the lesser curvature were ligated—a procedure which results mainly in a reduction of gastric secretion—twice the dose of cinchophen was required to produce chronic ulcer as compared with controls.

The fact that cinchophen ulcer is frequently at or near the pylorus prompted us (199) to investigate the extent to which a motility disturbance might be concerned in the genesis of these lesions. We found that the Rammstedt operation (pylorotomy) reduced the incidence of gastritis, hemorrhagic erosions, and ulceration which ordinarily follows the oral administration of the drug.

Circulatory Changes. Barco and Berti-Riboli (200) attributed the ulcerogenic effect of cinchophen to a discharge of histamine, "in the sense that this drug mobilizes histamine from its normal sites of deposit (liver, lungs, etc.)." In support of this view was the observation (201) that the capillaries of the dog's lip were altered during the intravenous administration of sodium salts of cinchophen, the changes consisting of vasodilatation and circulatory stasis. Ferreira (202, 374) also considers that the cinchophen ulcer is angiotoxic in origin. However, Loewy (203) reported that the development of these lesions seemed to be delayed by injections of histamine.

Attempts to Prevent or Ameliorate Cinchophen Ulcers. *Endocrines.* Farbman and his associates (204), attempting to simulate the beneficial effect of pregnancy on ulcer, administered cinchophen to six pregnant dogs and to nine dogs receiving daily injections of antuitrin-S. All of these animals, as well as the 19 nonpregnant controls receiving only

* These authors made the interesting observation that white Spitz dogs were, in their experience, more susceptible than other breeds to cinchophen ulcer.

cinchophen, developed ulcers. The ineffectiveness of treatment with antuitrin-S was confirmed by Slutzky et al. (205) and by Nasio (206).

According to Nasio (207), theelin had only partial prophylactic value against the development of ulcer in dogs receiving cinchophen, whereas stilbestrol (208) prevented the appearance of the ulcers in 100 per cent of male dogs and only 22 per cent of females. However, this treatment was not without deleterious effects on the gastric mucosa, which in most cases presented an appearance of granular hyperplasia and in some cases a congestive hemorrhagic gastritis. Similar results were observed (209) with Synapoidin, a mixture of chorionic gonadotropin and anterior pituitary extract. Slutzky et al. (205) reported that posterior pituitary extract exerted no effect on the development of cinchophen ulcers.

Vitamins. Nasio (210) could not demonstrate any beneficial effect of vitamin A, even in daily doses up to 360,000 units, on cinchophen ulcer. He observed (211) that thiamin chloride prevented weight loss to some extent in cinchophen-fed dogs, but it did not affect the development of ulcer. Essentially the same results were obtained with riboflavin (212). Berti-Riboli and Belgrano (213) reported that Vitamin C in large doses exhibited very little prophylactic value against cinchophen ulcers, but when combined with Vitamin B and adrenal cortical hormone, the results were more promising. Hueper (375) was unable to demonstrate any beneficial effect of Vitamin C, but according to Nasio (214), ascorbic acid in doses of 500 mg. daily exerted a protective action in 60 per cent of the dogs and reduced markedly the amount of bleeding in those animals which did develop ulcer. The same observer reported (215) that the ulceration produced by cinchophen is hastened and aggravated by nicotinic acid or nicotinamide; this was attributed to the marked inflammatory effect of the latter preparations themselves on the gastrointestinal mucosa. Nasio was particularly impressed (216) with the preventive action of calciferol on cinchophen ulcer. Administered in a dose of 5 mg. daily, calciferol prevented ulcers in 60 per cent of the animals. Most of those dogs which did develop ulcers were females. The author suggested that the prophylactic value of calciferol might be due to a depression of gastric secretion by the increase in serum calcium; but he does not report any determinations of either the serum calcium or the gastric secretion.

Neither naphthoquinone nor Vitamin K were found (217) to exert an effect against cinchophen ulcer in dogs (182).

Other Procedures. The development of cinchophen ulcer has been reported to be retarded by histamine (203), alkalies (203), Vichy water (219), gastric mucin (193), pectin (194), and by preparations of hog stomach and duodenum (302), but to be unaffected by gastroenterostomy (203), vagotomy (355), histidine (203), cholecystogastrostomy (219), liver

extract (214), or histamine (372). In our laboratory (286), the oral administration of desiccated, defatted hog duodenum and the parenteral administration of enterogastrone concentrates failed to protect dogs against cinchophen ulcer.

COMMENT. Anyone can demonstrate without difficulty that in dogs cinchophen, in a daily oral dose of 200 mg. per kilo, will usually cause chronic peptic ulcer within three weeks, usually in the pyloric part of the stomach. That the drug would probably have the same effect in humans is indicated by reports (376, 377, 555) of the occurrence of gastric ulcer in man in association with cinchophen poisoning. On the other hand, it is very difficult to produce cinchophen ulcer in rabbits, and practically impossible in rats. This apparent species difference should be investigated further.

The development of the cinchophen ulcer has been described adequately; the problem which still remains is to work out the mechanism. It is evident that the ulcerogenic effect depends on the administration of toxic doses, to which the dogs develop some measure of tolerance if they do not succumb in the first two or three weeks to perforation of an ulcer. At one time, we thought the ulcerogenic factor was contained in some impurity, rather than in the cinchophen itself. Prior to 1937, the cinchophen supplied by pharmaceutical houses had a grayish cream color. subsequently, a pure white cinchophen came into the market. It then developed that a higher dose or a much longer period of time was required to produce ulcer with "new" cinchophen than with "old" cinchophen. For example, we used to give 100 mg. per kilo of the earlier preparation, whereas, to obtain ulcers in the same period, we use 200 mg. per kilo of the newer drug. This is the reverse of what one would expect if the impurity were merely a diluent. Bradley (378) found that the "old" cinchophen contained phenylquinoline and an alkali-insoluble residue as contaminants, but neither of these materials was ulcerogenic. Working with another batch of "old" cinchophen, we (379) were able to separate the preparation into a crystalline white precipitate and a grayish residue by a hot alcohol extraction. Distressingly enough, however, the purified fraction proved to be more ulcerogenic in dogs than the contaminant. It is probable that some impurity acted to increase the toxicity of cinchophen, which was itself the ulcerogenic agent.

It seems sufficiently well established that the cinchophen ulcer is due mainly to some systemic disturbance. For example, we (199) found that the excretion of cinchophen into the stomach following the administration of the drug by routes other than the oral amounted to a maximum of 1.5 mg. per hour, indicating that the ulcers are probably not due to direct irritation of the gastric mucosa. The evidence seems to indicate that

hepatic damage is the most likely intermediate factor, particularly the glucuronic acid conjugating mechanism; if so, this is a highly selective form of liver impairment, for we (199) could demonstrate no change in the bilirubin clearance or serum phosphatase in dogs developing ulcer while receiving cinchophen. It is interesting to note that in the rabbit cinchophen is not a choleretic agent (553) nor, as noted above, does it cause ulcers in this species, whereas in the dog (and human) cinchophen is a powerful choleretic agent (554).

It may be that any one of a number of toxic agents, if administered in the proper dosage over a long period of time, would affect the stomach much as does cinchophen, without any question of the liver being involved. However, the only report of such an experiment which has come to our attention is that of Nakazawa (151), who fed a 4 per cent solution of o-amidoazotoluol in olive oil daily to 22 dogs over a period of 178 to 346 days. Chronic gastric ulcer was present in 10 dogs, duodenal ulcer in two, and ulcers of both the stomach and duodenum in three; in two cases, duodenal ulcers had perforated. But "cirrhotic changes" of the liver were present in almost all of the dogs which lived more than 200 days.

If the cinchophen effect is due in part to a disturbance of gastric function, we would judge from our experience that the motility disturbance is the only factor which has been shown to play a significant role. In dogs in which we severed the musculature at the pylorus to the extent that the mucosa pouted through (Rammstedt procedure), no ulcers developed in relation to the pyloric ring.

Production of Experimental Ulcer by the Principle of Immunization

Gastrotoxin. In 1903, Theohari and Babes (220) prepared a "gastrotoxin" by emulsifying ground gastric mucosa of dogs in a 1:1000 solution of salicylic acid. A small dose of this material injected subcutaneously was said to produce hypersecretion in dogs; a large dose intravenously resulted in rapid death, with hyperemia and hemorrhages throughout the gastrointestinal tract except the pyloric antrum and the colon. The authors were unable to account for the lesions in the intestine following the injection of the "specific gastrotoxin." Microscopic studies showed that the cytolytic action involved chiefly the gastric gland cells, with very little interstitial tissue reaction. This was confirmed by Lion and Francais (221). Loeper (222) reported that a rabbit receiving 16 cc. of an aqueous extract of pig's gastric mucosa developed three gastric ulcers, two of which perforated, within three days. He considered that the ulcers were not a direct result of the material injected, but resulted from the hypersecretion caused by the extract.

From 1904 to 1916, Bolton (68, 223–230) published a series of reports on the production of gastric ulcer by a specific gastrotoxin of the nature of a cytotoxin. He demonstrated that when stomach cells of a guinea pig were injected subcutaneously or intraperitoneally into a rabbit, the serum of the latter could cause hemorrhages and ulcerations of the stomach when injected into guinea pigs. It was further shown that this ulceration was brought about by the action of the gastric juice, because when 14 cc. of 4 per cent sodium bicarbonate solution was introduced into the stomach of the guinea pig before administration of the serum, no necrosis occurred. Similar experiments were carried out in cats. Later studies indicated that the gastrotoxin was not specific, since the same effects could be produced by hepatotoxin, enterotoxin, and hemolysin. However, Bolton considered this nonspecificity to be more important than if the action were specific, because it extends the etiological field of acute gastric ulceration, which in the human being one finds associated with many different diseases in which a general poisoning of the system is the chief phenomenon.

Miyagawa (231, 232), pointed out that the action of the hetero-gastrotoxin prepared by Bolton was duplicated by an isolysin or by an autolysin (prepared by sensitizing an animal against its own tissue) which the author prepared in rabbits. From his studies on autoserum, Miyagawa considered it reasonable that when an ulcer is produced in a part of the stomach wall by various causes, and a portion of the cells is necrosed and their components are absorbed, there will be a production of a special cytotoxin; this cytotoxin would have a toxic action not only on the cells of the stomach wall of another normal body, but on the cells of the other part of its own stomach wall, acting as a cause which renders the healing of the ulcer very difficult. In other words, he considered it not unreasonable to count the action of cytotoxin as a cause of the formation of the chronic ulcer. It will be seen that this concept is similar to the allergic theory of peptic ulcer.

Allergy or Anaphylaxis. Cesaris Demel (233), in 1923, conceived the idea that certain cases of ulcer may be on an anaphylactic basis; he suggested the following sequence of events as a working basis for this hypothesis:

> In some point of the mucosa there is a solution of continuity produced by trauma (as by a spicule of some rough ingesta); through this break, heterogeneous, incompletely digested proteins are absorbed, instituting the process of sensitization which is obtained experimentally by repeated injection of antigen. This sensitization proceeds to the point where a new entry of the heterogeneous protein produces vascular disturbances which lead to infiltration and edema of the mucosa, with ischemia, necrosis, and digestion of the dead tissue by the gastric juice, forming the ulcer. Such a train of events in the skin is called the Arthus phenomenon, and is followed by healing; not so in the stomach, where the lesion is constantly subjected to the action of gastric juice.

It was not long before this concept received partial support from the laboratory. We (234) demonstrated that local injections of protein into the gastric mucosa of sensitized rabbits and dogs resulted in acute ulcers. In the rabbit, the lesions healed completely in 12 days; in the dog 21 to 30 days were required for complete healing.

Anaphylactic ulcers have been produced in rabbits by Alessio (236), Coniglio (237), Vallone (238), Paolucci (239), Bernardini (240), Culmone (241), and Guerrisi (242). According to Vallone (238), anaphylactic ulcer does not resemble the human lesion in its histopathologic characteristics, although he considers that alterations produced in the human sensitized to diverse antigens might serve as a locus for the action of gastric juice. Paolucci (239) contended that sensitization could be produced in animals with acute lesions of the stomach by feeding foreign protein; if this is true, it supplies evidence for one of the weakest points in Demel's hypothesis.

Jahiel (243), emphasizing the intermittent nature of human gastrointestinal ulcerative disease, calls attention to the possible importance of an anaphylactic type of reaction which Gutmann has called "cellular memory." This phenomenon is demonstrated experimentally as follows: the injection of one half cc. of pure horse serum under the conjunctiva of a rabbit produces a transitory cellular infiltration; 20 days later, intravenous injection of two cc. of the same serum produces, within two hours, a conjunctival reaction identical with that produced by the previous local injection. Jahiel suggests that in peptic ulcer a similar mechanism may be operating, with the sensitization resulting from the absorption of abnormal endoproteins. That this suggestion may have some basis in fact is indicated by the interesting work of Walzer and his associates (244). These investigators sensitized the mucous membrane of macacus monkeys at various levels in the gastrointestinal tract by local injections of a reagin-bearing human serum, and they later observed the changes occurring at the site of injection when a sterile extract of the specific antigen was injected intravenously. In the stomach, an area of marked hyperemia and edema of the mucous membrane was observed at the sensitized site 10 minutes after the intravenous injection of the antigen. The entire reaction subsided within 45 minutes, however, and in none of the experiments did the process continue to the point of necrosis or superficial ulceration. Very similar results were obtained in rabbits by Mallone (245) and Niosi (246), who used bacterial filtrates for the injections.

Friesen and co-workers (385) used the same principle as that employed by Walzer. They obtained serum from a horse previously sensitized to five different antigens and injected it in dogs into the gastroduodenal submucosa or into the arteries supplying the stomach and duodenum. Each day thereafter one of the antigens to which the horse

serum contained antibodies was injected parenterally in the dogs, thereby producing a sustained allergic reaction in the sensitized area. Edema and hemorrhage occurred and, in a few instances, the process progressed to actual ulceration. One series of dogs was given histamine in beeswax in addition to the sensitizing procedure and, in these, ulceration of the areas undergoing the allergic reaction occurred regularly.

Hayashi and Kato (247) produced anaphylactic shock in guinea pigs and found gastric lesions in a significant percentage of cases. When the gastric spasm was prolonged by repeated mild shocking doses, ulcers with a tendency to chronicity were produced. Berti-Riboli (391) concluded, from experiments in dogs receiving cinchophen after the reticuloendothelial system was blocked with trypan blue, that gastric ulcer represents the localization in the stomach of an allergic state of the whole organism.

COMMENT. Cesaris Demel (235) hailed our experimental studies on the production of gastric ulcer by local anaphylaxis (234) as the "beginning of a series of experimental and clinical observations in confirmation of the anaphylactic theory of round ulcer already proposed by me in 1923." This was a much more enthusiastic interpretation than we ourselves could make, because none of the ulcers we produced by this method ever became chronic. The same results were obtained by the numerous Italian investigators of the problem, all of whom worked with rabbits.

At the site of injection of the specific protein in the gastric mucosa of sensitized rabbits, there developed an orderly sequence of pathologic changes. For from one to two days, there was an extensive area of local passive hyperemia and edema. As this slowly disappeared, the central portion of the area became indurated and necrotic. In from three to six days, this area ulcerated sharply, cleanly, and regularly. The margins of the ulcer gradually became thicker, often with mucosal proliferation, and rolled in over the base. Healing was usually complete by 12 days. Rarely did an ulcer remain unhealed much longer. The fundic lesions were practically identical with the pyloric.

In dogs, our experiments were carried out in pyloric pouches, in which the pathologic changes could be observed continuously. Within two minutes after injection of the provocative dose, the pouch contracted violently and everted. The mucosa became blanched, then cyanotic and markedly edematous. These last changes were most severe at the area of injection. The next day the pouch as a whole had recovered, but at the site of injection there was a large, bluish black, dried area definitely dilimited by a narrow red line of active hyperemia. On the third day, the central portion of the area turned grayish yellow. By the sixth day, the necrotic mucosa had sloughed out, leaving a punched-out ulcer with a

granulating base. The depth of the lesion varied greatly. The edges and base of the ulcer became firm. The ulcer deepened as the edges increased in thickness and began to roll in toward the base. The base was covered later with a glistening, fragile membrane. Contrary to Vallone (238), we found that the ulcer at this stage is in all respects comparable in microscopic structure to acute peptic ulcer in humans; there is a mild inflammatory reaction with connective tissue proliferation. Healing time ranged from 21 to 30 days.

If the pouch was reinjected with the specific protein at any time within three days after the first provocative injection there was no reaction. A second injection after three days usually yielded a more or less severe reaction; but after four days, reinjection always produced another ulcer. This could be repeated until the pouch was fairly riddled with ulcers, *but the ulcers always healed.*

If the reinjections were made in the base or edge of the ulcers, they extended and became terraced; but these four-day reactions became progressively less severe than the preceding ones and healed more rapidly, so that the total healing time of the original ulcer was not appreciably prolonged.

The production and course of local anaphylactic ulcers produced in the gastric mucosa *in situ* was practically identical with that of the ulcers in the gastric mucosa of pyloric pouches. Healing time was not affected by the acid or the motility.

Despite the failure to produce chronic peptic ulcer experimentally by anaphylactic reactions, the possibility remains that such a factor may be concerned in certain instances of human peptic ulcer. The mechanism suggested by Miyagawa (231, 232), viz., that the individual may be sensitized by the absorption of protein from the necrotic tissue of an acute lesion of the stomach, either does not occur in experimental animals or, if it does occur, it certainly does not interfere with healing of the acute lesion. It is extremely doubtful whether such a mechanism operates in the human. We have not checked Paolucci's (239) claim that the feeding of foreign protein to animals with acute lesions of the stomach will result in sensitization, and it remains to be determined whether this report can be confirmed. If his observation is correct, then it would have to be shown that subsequent feeding of the same protein could result in ulceration. Otherwise, we do not see how the results of any of the experimental work hitherto reported can be rendered applicable to the initiation of chronic ulcer in man.

Crohn and Shwartzman (392) called attention to the possibility that ulcer recurrences associated with upper respiratory infection may be a manifestation of the Shwartzman phenomenon. As these authors visualize

the process, bacteria which invade an ulcer confer upon the tissues of th lesion a state of lasting reactivity. "Once this state of reactivity exis viruses and bacteria-producing infections in organs distant from th gastric ulcer may be able to produce injury in the ulcer by way of th general circulation." This is an important concept, and one which shou be investigated further. In the discussion of infection (p. 266), we note that all attempts to produce chronicity by direct infection of acute ulce were unsuccessful. However, it has not, to our knowledge, been dete mined whether the introduction of organisms into experimental acu ulcers establishes a state of reactivity such that, after the ulcer has heale the systemic introduction of the same or similar organisms might cau a recurrence.

Nothhaas (393) has been advocating the belief that peptic ulcer is d to a sensitivity to the split products of animal protein. In his opinion, th reason for recurrence in patients who are rendered symptom-free on Sipp management is the resumption of meat in the diet. In those not relieve by the Sippy regime, there is an allergy to milk and eggs. The princip experimental evidence which Nothhaas claims to have obtained for h view requires confirmation. He observed (394) that after a meat-free die the ingestion of meat is followed by an increased peripheral blood flow ulcer patients, but not in controls, as determined by (1) the increas warmth of the hand, and (2) the decreased duration of the dermograph reaction. He construes these observations as indicating a decreased circul tion in the stomach, predisposing to ulceration.

On theoretic grounds, there is no good reason to doubt that an allerg reaction of the urticarial type may take place in the gastroduoden mucosa, just as it does in other mucous membranes and in the skin. B it still does not explain adequately how a chronic ulcer may result fro the allergic process alone. The fact that a chronic lesion has not be produced by allergic means in the experimental animal does not rule o the possibility that it does occur in human beings. A number of chro diseases of humans are quite clearly established as being allergic in ori even though no experimental counterpart of the chronic form of any these conditions has been produced. On the other hand, although th possibility exists, there is no good evidence to indicate that peptic ul in man is an allergic disease.

Nutritional Disturbances

Nonspecific or Multiple Dietary Deficiency. Pappenheimer a Larimore (248) called attention to the occurrence of ulcerous lesions the stomach in rats maintained on a deficient diet. The authors poin out that rats on improper diets tend to eat hair, which may play

portant role in causing the lesions, either as a mechanical irritant or as e carrier of an infected agent. Magee et al. (249) noted peptic lesions rying from superficial erosions to perforating ulcer in the stomach and odenum of guinea pigs on a deficient diet (plus unilateral adrenalec-my); since these lesions were found in association with stasis in the cum or proximal colon, the authors suggested that the formation of stamine might be responsible.

Impressed by the high incidence of gastric ulcer in Madras and of odenal ulcer in Travancore, McCarrison (9) investigated the effect of ts used in these districts of India on albino rats. The experiment was 675 days duration.

In the group of rats maintained on the Madrassi diet (rice, red pper, tamarind, fish, and rice water), gastric ulcer developed in 11.1 r cent; in those on the Travancorian diet (tapioca root, rice, fish, red pper, rice water), gastric ulcer was present in 27.7 per cent and marked odenitis in 11.1 per cent. More recently, Orr and Rao (250) fed the avancorian type of diet to a group of dogs. No ulcers developed but generation of the Meissner-Auerbach plexuses was noted in the his-ogic studies of the stomachs. These pathologic changes were interpreted being analogous to similar findings occurring in surgical specimens of man stomachs resected for the treatment of ulcer in natives of southern ia. Dogra (354) fed monkeys a diet identical with that used by the er-susceptible population in south India, and although the animals imately died of inanition, none developed ulcers.

Morris et al. (395) observed occasional gastric ulcers in rats which re fed an apparently adequate diet containing 50 per cent heated lard. ny of these animals developed fatty, cirrhotic livers. However, it was determined whether the nutritional disturbance provoked by the ted lard was due to interference with the utilization of some essential dstuff in the diet or to a toxic product formed in the heating of the lard.

The effect of hunger on the occurrence of gastric ulcer in dogs was stigated by Bogoras (251). Five dogs were given 100 Gm. of bread per every fourth day until death. Multiple erosions and ulcers of the nach were found in four animals surviving from 14 to 30 days; gastric lysis during the hunger periods (studied in one dog) showed high acid ues.

In rats, ulcers of the prostomach were reported to occur as a result of ding and starving on alternate days (252), or within six days of starva-(255); ulcerations of the glandular stomach also have been reported 5, 257) during complete deprivation or marked curtailment in the ntity of food. The lesions have been ameliorated or prevented by ain foods, such as dextrose (255), or by any type of food (256).

VITAMIN DEFICIENCY. *Vitamin A.* Manville (258) reported that 60 per cent of white rats on a Vitamin A deficient diet developed gastric ulcers and peptic erosions; these were associated with a reduction in the amount of mucus secreted in the stomach without a corresponding diminution in acid production. The feeding of mucin did not ameliorate the nutritional status of the rats, but seemed to have some preventive effect on the stomach lesions. Olcott (396) did not observe ulcers in A-deficient dogs. According to Harris et al. (398), a deficiency of Vitamin A (or B_6, or essential fatty acid) did not in itself cause lesions in the forestomach of rats; rather, the ulcerations appeared only during the curative period in which the specific nutrient was fed. The administration of alpha tocopherol (Vitamin A sparing substance) during the recovery period protected against the development of the lesions. The authors explained the phenomenon as follows:

> The epithelium of the forestomach becomes functionally impaired by the deficiency but no anatomical lesion develops because of adaptation of the organism to the low level of food intake and probably because of decreased secretion of HCl-pepsin. Administration of the missing essential factor induces food intake and weight gain. Unless adequate tocopherol is also administered, the functionally abnormal epithelium is unable to resist the acid-pepsin with which it is in contact and as a result lesions are produced.

Vitamin B. Production of gastric ulcer in five of eight rats on a B-deficient diet was reported by Sure and Thatcher (259), and in a further study (260), the authors were led to believe that the Vitamin G factor was the important component in protecting the gastric mucosa in rats. Howes and Vivier (261) noted that on a diet consisting of flour and a salt mixture, young rats in particular were prone to develop ulcerations of the rumen of the stomach, and that the addition of yeast to the diet had a protective action. In albino rats on a Vitamin B deficient diet, Dalldorf and Kellogg (262) noted gastric ulcers in 73 per cent of the animals. Ten per cent of the lesions were chronic and indurated and these were generally located along the lesser curvature. Simpson (263) was unable to produce gastric ulcers in rats when care was exercised to prevent the occurrence of deficiencies other than thiamin. Shay et al. (397) observed ulcers of the corpus (i.e., glandular portion) of the stomach in 100 per cent of rats on a diet deficient in thiamin, in 50 per cent of rats on a diet restricted in calories so as to produce a weight loss comparable to that of the thiamin-deficient group, and in none of the rats on an unrestricted normal diet. Not only was the incidence of ulceration greater in the rats suffering from thiamin deprivation than in those with nonspecific deficiency, but the lesions were more severe. The authors concluded that while the specific deficiency was not the sole factor concerned in the ulcerations, it imposed an addi-

tional factor; from the results of their studies on gastric secretion in these rats, they believe that the additional factor is an increased secretion of active gastric juice.

Various types of acute gastric lesions were observed by Schiödt (264) in rats maintained on diets deficient in Vitamin B complex. In the experiments of Fouts et al. (399), a deficiency of Factor II (chick anti-dermatitis factor) caused fatty livers in seven dogs, one of which had a penetrating ulcer of the lesser curvature in addition to numerous gastroduodenal erosions. Further studies (400) in which puppies were fed a low protein diet containing all of the recognized basic supplements were carried out. These animals developed severe fatty changes in the liver and chronic ulcers of the stomach and duodenum; however, the fact that an increase in the protein level of the diet prevented the lesions indicates that they are probably not specific.

Rao (265) placed 12 puppies on a Vitamin B complex deficient diet consisting of rice and milk with supplements of Vitamins A, D, and C. Within 21 to 119 days the animals succumbed; two animals had chronic gastric ulcer; one had a healed pyloric ulcer; and one had three ulcers in the first portion of the duodenum. Rao recognized that the anorexia occurring in these animals might have contributed to the development of the ulcers.

According to Chittenden and Underhill (266), a certain number of the dogs placed on a pellagra-producing diet died characteristically following a sudden onset of convulsions, and in this group of animals the only visible abnormality of the alimentary tract was the presence of one or more large duodenal ulcers. One cannot be certain, however, that these were really ulcers.

Vitamin C. In one of the classic reports in the field of vitamin research, Holst and Frolich (267) described the production in guinea pigs of a disease identical with human scurvy. In some of the scorbutic animals, autopsy revealed small hemorrhages in the gastric mucosa and occasionally perforated duodenal ulcers. This observation was reinvestigated and confirmed 25 years later by McCarrison (9). Smith and McConkey (268) reported that when the stomach and duodenum of adult guinea pigs were surgically traumatized, complete healing occurred in those animals receiving an adequate diet, while ulcers developed in those kept scorbutic. Hanke (269) stated that erosions of the pyloric mucous membrane were present in 50 per cent of guinea pigs on a C-deficient diet.

*Anti-gizzard Erosion Factor.** In the course of the investigations leading

* For reviews of the literature on the anti-gizzard erosion factor, see Jukes and Almquist (295), and Dam and Segal (401).

to the discovery and isolation of the anti-hemorrhagic factor for chicks (Vitamin K), it was observed that chicks on deficient diets frequently develop erosions of the gizzard lining (270–275). It was soon learned, however, that the occurrence of the gizzard lesions was not closely correlated with the hemorrhagic syndrome, since Vitamin K prevents hemorrhages without preventing the gizzard erosions (276–278). Accordingly, it has been concluded that the gizzard lesions are caused by the deficiency in the diet of a food factor not identical with any of the known vitamins. Simplified experimental diets low in fat or free of green plant tissue are most conducive to the formation of these lesions (277, 279). No correlation has been found between the anti-gizzard erosion factor and growth-promoting factors.

There is general agreement that the lesions of the gizzard are the result of dietary deficiency but the reports on the properties of the preventive factor are widely divergent. It has been suggested that the anti-erosion factor might be identical with the hypothetic "Vitamin B_3" (280) but this could not be confirmed by Almquist and his co-workers, who have demonstrated repeatedly that the factor is fat-soluble and distinct from any of the other fat-soluble vitamins (276, 277, 281, 282).

One report (283) states that chondroitin prevents gizzard erosions but in other investigations this substance was not found to be appreciably active (284–286). Dam and Segal (401) have made an extensive systematic investigation of the effects of various substances added to the basal gizzard erosion diet. We (431) have tried intestinal extracts, without success.

A new aspect of the problem of the nature of the anti-erosion factor was provided in the finding that bile and bile acids in the diet of the chick will prevent lesions in the gizzard lining very effectively (287). Cholic acid was the most active of the natural bile acids tested, while dehydrocholic acid, an artificial derivative, was almost equally active (288). The activity of cholic acid in the prevention and cure of gizzard lesions has been confirmed (289). Hog bile, which contains very little cholic acid, is comparatively ineffective (286).

It was determined that the concentration of cholic acid in chick gall bladder bile and the amount of cholic acid in combination with the gizzard lining are reduced in the presence of erosions. The suggestion has therefore been made that any condition which might inhibit the normal secretion of bile, directly or indirectly, might lead to gizzard erosion (288). It has been further hypothesized that, since practical chick diets which are not conducive to gizzard erosion do not contain appreciable amounts of cholic acid, the source of the erosion-preventing action of these diets may be some precursor required by the chick for the normal

secretion of bile acids (288). Whole milk and skim milk, given in place of drinking water, reduce the incidence and severity of gizzard erosions and increase the amount of cholic acid present in the gall bladder of the chick. The active factor remains in liquid milk after boiling and distillation but is absent in commercially prepared dried milk products (290). In addition, whey and protein-free milk exhibit an activity similar to that of skim milk (291).

The feeding of cinchophen to chicks will produce lesions of the gizzard which resemble closely those in chicks on a gizzard-factor-deficient diet (p. 293) (180, 181).

The gizzard lesions have been stated to originate as small hemorrhages in the capillaries of the submucosa which have been considered to be due to failure of bile to pass from the gall bladder into the duodenum, as indicated by the absence of bile in the cystic duct (292, 293).

Cheney (296) investigated the relation of gastric acidity to the development of gizzard erosions. He found that 13 chicks which developed gizzard erosions secreted in response to histamine gastric juice with an average acidity 16.8 degrees higher than normals and 24.3 degrees higher than those on the deficient diet which did not develop erosions. However, Dam and Segal (401) found the fasting secretion of normal chicks to be slightly more acid than the secretion of chicks reared on various artificial diets regardless of whether or not they are ulcerogenic, and the fasting acidity of chicks on ulcer-producing diets was no higher than that of chicks on normal diets. The same observers have shown that the chick gizzard erosion diet is not ulcerogenic in rats within the 94 days of their observation period. Similar studies would be desirable in other laboratory animals, particularly since it has been reported (294) that the anti-gizzard erosion factor is efficacious in the treatment of peptic ulcer in man.

Calcium Deficiency. Zucker and Berg (297, 298) found that rats which were placed on a calcium-free diet for 28 days with precaution taken to insure against other deficiencies due to lowered food intake develop a distinctive type of ulcer. These lesions are restricted to the antrum and show a unique histologic form, being sharply punched out with proliferative edges. Prolongation of the deficiency increases the ulcerative and hyperplastic character of the lesions but does not lead to penetration. These experiments are of special interest because the diets were carefully controlled by paired feeding to show that calcium deficiency was the only factor responsible for the lesions.

Protein Deficiency. Considerable work has been done by Hoelzel and DaCosta (252–254) on the relation of protein deficiency to ulceration of the prostomach in rats. These authors have shown that a high incidence of such lesions results when protein is withheld, and that the frequency

of the lesions is reduced when an incomplete protein, such as gelatin, is added to the diet; it appears that the ulcerations are not associated with any significant increase in the gastric acidity, but that pylorospasm may be an important factor. Production of gastric ulcers in rats by feeding protein-deficient diets has also been reported by Orten (426).

Weech and Paige (299) fed dogs a diet sufficiently low in protein to produce hypoproteinemia and edema in one to three months. In 22 of these dogs, surviving an average of 90 days, autopsy revealed true peptic ulcer in eight (36 per cent) and erosions in five (23 per cent). There was no correlation between the degree of emaciation or of anemia and the frequency of ulcer. A careful study of the factors involved in the development of ulcers in dogs maintained on protein-deficient diets has been made by Li and Freeman (300). Thirty-two dogs were maintained on a diet which supplied 40 cal. per pound of body weight daily and was devoid of protein save for that contained in the yeast which made up 5 per cent of the diet. Fifteen of the 32 dogs had ulcers; 13 had gastric ulcers near the pyloric sphincter; and two had ulcerations of the duodenum. The survival period varied from six to 22 weeks; but no animal that survived less than 12 weeks had an ulcer. Diets high and low in fat, with or without cholesterol or added bile salts, caused a similar incidence of ulcer. Dye clearance by the liver, elevation of serum phosphatase, and fattiness of the liver could not be correlated with the frequency of ulcer. These experiments suggest that a very high incidence of ulcer could be induced in dogs by using a diet which produced a less severe protein deficiency so that the survival time would be increased.

Comment. There should be no disagreement with the contention that nutritional deficiencies sufficiently advanced to interfere with maintenance of body tissues may predispose to ulceration of the gastrointestinal mucosa. Moreover, the importance of including adequate protein and vitamins in the diet of the ulcer patient, because of their relations to wound healing, would seem obvious. The question of significance in the problem of peptic ulcer is whether a specific deficiency can be shown to be of etiologic importance in man. From this viewpoint, an intelligent evaluation of the experimental work seems to us impossible at the present time.

One of the principle difficulties lies in the interpretation of the numerous reports of the occurrence of gastric lesions in rats fed various types of experimental diets. Anyone contemplating or conducting such experiments should familiarize himself with the work of Berg (301).

In the first place, the stomach of the rat possesses certain anatomic characteristics which must be borne in mind in considering the significance of the lesions. The cardiac portion of the rat stomach consists of a thin pouch lined by squamous epithelium and designated variously as the

rumen, prostomach, or forestomach. The homologous structure in the human stomach might be considered to be the cardiac gland area, a narrow ring of mucosa surrounding the esophageal opening. However, the cardiac glands of the human are simple tubular mucinous glands and not squamous epithelium like the lining of the rat's rumen. Thus, a large number of the experimentally induced lesions in the rat stomach occur in the portion to which there is no exact human homologue. Nevertheless, there is evidence to indicate that these lesions are in some cases produced by peptic digestion, so they cannot be considered entirely without significance.

Secondly, the exact nature of these gastric lesions in rats is often difficult to evaluate. Seldom has good evidence for the existence of chronic indurated ulcer in rats been presented. As was pointed out in Chapter 1, the significance of acute gastric defects in the study of experimental ulcer must always be approached with circumspection. Another, and no less important, difficulty encountered in the interpretation of gastric lesions in the rat is the frequent association of neoplastic changes with the ulcerous defects. This association of proliferative and ulcerative processes appears to be due to at least two factors; viz., the tendency of the mucosa at the edge of the ulcer to undergo proliferation, and the tendency of primary proliferative lesions (e.g. those produced by carcinogens) to undergo peptic ulceration. Both of these tendencies occur to a varying degree in other experimental animals and, indeed, even in man; however, they appear to be more pronounced in the rat than in other species. Because of these peculiarities, the literature on experimental peptic ulcer and experimental gastric cancer in the rat have become interrelated.

The third factor which makes interpretation of results of diet experiments in rats difficult is a failing encountered in many experiments in nutrition. This factor is the failure to control the experiments in such a manner that the deficiency of a single dietary factor can be recognized as the cause of the lesions. In many cases, multiple deficiencies result from decreased total intake of food. Only by paired feeding in which the difference in the quantity and quality of the food ingested by test and control groups is accurately known can this difficulty be obviated. This has been accomplished in very few of the published experiments.

In many cases, the exact location and character of the lesions is not clearly set forth in the published reports. In such instances, the data have only suggestive value.

These limitations must be considered in evaluating the reports cited here. For example, Dogra (354) gave three good reasons for questioning McCarrison's conclusion that the presence of ulcerations in rats fed certain deficiency diets proved that a dietetic factor was concerned in the

etiology of peptic ulcer in southern India. Dogra objected that (1) the observed lesions were apparently of an acute nature; (2) some 40 per cent of the rats in which ulcerations were present died of pneumonia, which in itself could account for the stomach lesions; (3) the problem in south India is one of a chronic, slowly developing ulcer of the first part of the duodenum, and not acute ulcers of the stomach. Therefore, the experimental work did not produce a pathologic process similar to that occurring in man.

One would assume, *a priori*, that in a nutritionally deficient state the functions of the stomach, if affected at all, would be diminished. The evidence on this point is relatively scant and unsatisfactory.

Manville (258) stated that in A-deficient rats the pH of the gastric juice was 2.5 to 3.0, as compared with 3.4 in controls, but Dyer and Roe (403) could demonstrate no significant effect of A-deficiency on the volume, acidity, pepsin, or mucin of mecholyl-stimulated secretion in rats. Herrin (402) could find no decrease in the histamine-stimulated volume or acidity of the gastric secretion in four dogs during avitaminosis A but observed a delayed gastric emptying in seven of the 15 dogs studied.

Reports on the effects of deprivation of one or more of the components of the B complex indicate that any change in the gastric secretory volume, or acidity, or both, are in the direction of a decrease in man (404–406), dog (407–410), rat (264, 412), and pigeon (413). However, Shay and his associates (397) have reported that in the presence of acute severe thiamin deficiency in rats, there is a much greater volume of spontaneous gastric secretion than is found in controls, while the acidity, peptic power, and total chloride concentration remain unchanged. In more advanced stages of thiamin depletion, the acidity decreases; the volume remains high and the peptic activity unchanged. The authors considered the hypersecretion to be responsible for the ulcerations developing in these rats.

No more conclusive than the rat experiments are the many observations reported on the erosion of the gizzards of chicks. There is no way of knowing at the present time whether the anti-gizzard erosion factor, if there be such an entity, will prove to be of any significance beyond the species which is affected by the deficiency. Thus far, there is no evidence that this deficiency affects other laboratory animals. To a certain extent, gizzard lesions are a "normal" accompaniment of the development of chicks, for hemorrhages appear in the gizzards of embryos by the 20th day of incubation (427); gizzard lesions are only exceptionally absent in day-old chicks (428, 429) and usually do not progress in severity during the first week regardless of the diet (430).

We are not familiar with any publication showing that a specific vitamin deficiency is concerned in human peptic ulcer. Attention has

been directed chiefly at Vitamin C, which has been reported as normal (414–416) or as below normal because of restricted ulcer diets (417–423). For example, Ebbesen and Rasmussen (416) found the serum ascorbic acid concentration normal in 63 patients on admission to the hospital for treatment of peptic ulcer and gastroduodenitis. Further determinations in 35 cases while on ulcer management showed a marked fall. This is precisely what one would expect, since milk, cream, eggs, and cereals are extremely poor sources of Vitamin C (425), and the level of this vitamin in the blood is dependent on the Vitamin C content of the recent diet (424).

There is suggestive evidence that the peptic ulcers prevalent in certain parts of India and in Abyssinia are attributable to a nutritional deficiency. From the information available, it appears that the deficiency is a multiple one, involving proteins and Vitamins A and B. According to Somervell (368), present conditions in India do not permit treatment of the disease by correcting the deficiency, and he therefore "fits the stomach to the diet" by surgery. Bergsma (8) makes essentially the same statement about the natives of Abyssinia. We cannot understand why, if these ulcers are due to inadequate diets, they should be managed successfully, as apparently they are, by gastroenterostomy; one would expect a high rate of postoperative jejunal ulcer. Some experimental evidence might be obtained on this point by determining the effect of gastroenterostomy on the ulcers which occur in dogs on prolonged protein deficiency.

Endocrine Disturbances

Adrenal Gland. In 1905, Cioffi (303) reported that in rabbits dying about a month after the second stage of bilateral adrenalectomy, hemorrhages and ulcerations were present throughout the stomach. These observations have been confirmed repeatedly (14, 61, 71, 306, 308–311, 313, 343–346) (Table 13). Only one report (304) denies the occurrence of gastroduodenal lesions after adrenalectomy, although Chakovitch et al. (305) noted only one instance of ulcer in 35 dogs surviving up to five days after removal of both adrenals. On the other hand, there are only two reports (307, 308) of true chronic peptic ulcer following adrenalectomy.

Rogoff and Stewart (306, 307) observed that in pregnant dogs, in which the survival period following bilateral adrenalectomy was longer than in non-pregnant controls, there was a higher incidence of ulcer; furthermore, these ulcers tended more toward chronicity. Oldberg (308) performed pedicle-transplants of the adrenal gland on 15 dogs, four of which lived in a state of chronic adrenal insufficiency for from 44 days to 4 months; when the pedicle of the transplant was sectioned, one of the animals died on the sixth day with "kissing" ulcers of the duodenum, one

of which had perforated and caused death. These are apparently the only significant observations reported to date which point to a relationship between the adrenals and peptic ulcer.

Table 13

AUTHORS REPORTING ACUTE LESIONS IN STOMACH AND/OR DUODENUM FOLLOWING BILATERAL ADRENALECTOMY

Observers	*Date of Observations*	*Animals*	*Observation Period*
Cioffi (303)	1905	rabbits	1 mo.
Gibelli (14)	1908	dogs rabbits	4 hr.–27 da.
Finzi (309)	1913	rabbits dogs	1–20 hr.
Elliott (148)	1914	cats	9–10 da.
Mann (311, 312)	1916	dogs & cats	2–8 hr.
Ivy (61)	1920	dogs	10–72 hr.
Katayama (71)	1920	rabbits	Few hr.–17 da.
Banting (344)	1926	dogs	1–10 da.
Rogoff* (306, 307)	1926	dog	Up to 59 da.
Oldberg* (308)	1929	dogs	44 da.–14 mo.
Levy (345)	1930	cat	
McLaughlin† (313)	1933	dogs	1 wk.–1 mo.
Freud (346)	1935	dogs	24–30 hr.
Imperati (310, 332)	1936	dogs	16–31 da.

* Reported chronic ulcer.

† Bilateral adrenal damage produced by electric cautery.

Mechanism of Formation of Gastroduodenal Lesions after Adrenalectomy. Finzi (309) attempted to prove that the changes were due to the loss of the adrenal glands, and not to operative manipulation of the nerves, by transplanting adrenals into adrenalectomized rabbits, but this was apparently successful in only one animal. Imperati (310) stated that the daily subcutaneous administration of adrenalin and cortical hormone to a group of nine dogs for 21 to 30 days after adrenalectomy completely prevented the appearance of lesions in any part of the gastrointestinal tract. Mann (311, 312) pointed out that the ulcers seemed to develop in the terminal stages of adrenal insufficiency; in 10 experiments in which sodium bicarbonate was administered during this period, only one of the animals had ulcers, indicating that acid is at least one of the factors in the development of these lesions. McLaughlin (313) stated, without giving

any data, that gastric analysis in three dogs showed that the acidity was not definitely altered by adrenalectomy. (During the operation for adrenalectomy, the splanchnic nerves are irritated or traumatized.)

The probability is that an explanation of the *acute* lesions following adrenalectomy lies in the circulatory impairment accompanying the state of shock which develops in these animals. The cause of the chronic perforating ulcers is unknown.

Thyroid and Parathyroid. In 19 of 23 thyroparathyroidectomized dogs, Carlson and Jacobson (314) found marked hyperemia, congestion, and hemorrhagic areas in the mucosa, particularly in the pyloric end of the stomach and of the duodenum; and in a number of cases, there were more or less extensive ulcers in the pyloric and duodenal mucosa. These findings were attributed to a deficiency of the parathyroid secretion. In 24 dogs dying of parathyroid tetany, we (61) found one acute ulcer of the stomach and three of the duodenum. Superficial erosions of the stomach were noted in 13 of these dogs, and of the duodenum in 15, which lived from three to 20 days, and in which the incidence of the lesions was proportional to the length of survival. A very interesting case of chronic gastric and duodenal ulcer in a dog with carcinoma of the thyroid was presented by Mann (315).

Mechanism of Ulceration Following Thyroparathyroidectomy. When it came to the attention of Silvestri (316) that ulcers were reported to follow removal of the parathyroids, he recalled never having observed ulceration in thyroparathyroidectomized dogs and rabbits if these animals were also castrated; he postulated that castration neutralizes the vagotonia resulting from removal of the sympathetic-acting endocrine glands, as the thyroid or adrenal. But Keropian (317) reported that the incidence of ulcer in thyroparathyroidectomized dogs was not altered by simultaneous castration, but was decreased by bilateral vagotomy. Yet, according to Schiffrin (318), thyroparathyroidectomy in dogs is followed by an increase in the volume of secretion from a gastric pouch in response to various stimuli, regardless of whether the pouch has vagal innervation. Constant (319) believed, on the basis of meager evidence, that stagnation of the gastric contents resulting from parathyroidectomy provides conditions favorable to ulcer formation; but Winkelstein and Ziegler (320) demonstrated that an artificially produced ulcer on the lesser curvature of the pyloric antrum healed completely in spite of thyroparathyroidectomy and the existence of latent tetany. Wu (321) found that total thyroidectomy did not influence the development of ulcer in Mann-Williamson dogs.

The publications of Friedman (322) attributed significance to the adrenal, thyroid, and parathyroid glands in the etiology of ulcer; from a

complex series of experiments consisting of adrenalectomies, thyroidectomies, and administration of adrenalin and thyroid extract, the author considered it

> probable that gastric lesions might be dependent upon adrenal insufficiency as well as upon an excess of thyroid gland; duodenal lesions, on the contrary, depend upon thyroid hypofunction as well as upon excess of adrenalin. Gastric and duodenal lesions might be dependent upon the alternating effect of hypo- and hyperfunction of the adrenals.

There is no experimental or clinical evidence in support of this hypothesis.

Animal experiments on the relation of the thyroid and parathyroid glands to peptic ulcer have been unsatisfactory principally because of the technical difficulty in eliminating these glands separately.

Parathyroid insufficiency is so relatively infrequent clinically that one would hardly expect it to be concerned in the ordinary case of peptic ulcer. Disturbances of the thyroid, on the other hand, are common and, because of the alleged similarity of facial expression and other characteristics between hyperthyroid and ulcer patients, a relationship between the two conditions has been suggested. The fact is that the incidence of peptic ulcer in association with hyperthyroidism is lower than in the population at large.

Brown et al. (432) reviewed the literature on gastric secretion and motility in hyperthyroidism and contributed extensive studies of their own. The findings of previous investigators were conflicting, but most authors reported a decreased gastric secretion in thyrotoxicosis, both clinical and experimental. Brown and his associates observed a significant increase in the incidence of achlorhydria and a significant delay in gastric emptying.

Pituitary. Considering the relative frequency with which pituitary glands are being removed in experimental animals throughout the world, it is surprising that more data are not available on the incidence of gastrointestinal lesions following hypophysectomy. Of 18 hypophysectomized dogs observed by Keller, D'Amour, and Hare (323), eight developed gastroduodenal changes similar to those described by Keller et al. (324) after hypothalamic lesions, viz., hemorrhagic erosions and acute ulcerations. Four of the dogs died within 24 hours; the remaining four died of cachexia from four to 17 days after operation. Serial sections showed that the hypothalamus was not injured in these dogs. Occasional small gastric erosions following hypophysectomy in a large number of rats and cats were reported by Dodds et al. (325). Metz and Lackey (326) observed heightened gastric motility and spasticity and increased redness of the gastric mucosa following removal of the posterior pituitary in dogs.

It has been shown by Dodds and associates (325–328), repeatedly confirmed (175, 329–336), and only once denied (337) that injection of large doses of posterior lobe extracts subcutaneously or intravenously into

experimental animals produces an ulcerative lesion of the stomach. We (411) injected subcutaneously a series of dogs hourly day and night for two weeks with pituitrin in doses adequate to cause almost complete anuria and a urine specific gravity of 1.060 to 1.070 without the occurrence of ulcer. Dodds has stated that the active extracts inhibit the gastric secretory response to histamine in rabbits. Several investigators are agreed that the ulcer-producing property is contained in the pressor, but not in the oxytocic fraction. However, Metz and Lackey, on the basis of findings mentioned in the previous paragraph, have recommended the use of posterior pituitary powder in the treatment of peptic ulcer.

Seeking some correlation between the integrity of the gastrointestinal mucosa and the pituitary gland, Laporta, Pepe, and Marinelli (338) could find no changes in the pituitaries of dogs with superficial erosions of the fundus of the stomach after an intestinal short-circuiting operation.

Winkelstein (434) reported that the majority of cases of duodenal ulcer in boys between 11 and 17 years of age was associated with signs of a pituitary disturbance. Observations of Kaulbersz et al. (545) indicated that hypophysectomy in dogs is followed by a reduction or absence of the gastric secretory depressant in the urine (see Chapter 13).

Sex Hormones. Impressed with the clinical observation that pregnancy has a beneficial effect on peptic ulcer, Sandweiss, Saltzstein, and Farbman (339) tested the effect of hormones abundant during pregnancy on the incidence and healing of ulcers in M-W dogs. Theelin and A.P.L. hormone (both obtained from the urine of pregnancy) were administered separately in two groups of animals. The incidence of ulcer was 100 per cent in 15 controls, 100 per cent in 15 dogs each receiving 1000 I.U. of theelin in oil subcutaneously daily until death, and only 47 per cent in 15 dogs receiving 1 cc. of antuitrin-S daily. In the latter group, signs of healing were observed in four of the seven dogs dying with ulcer. The survival period in the A.P.L.-treated group ranged from 16 to 106 days, with only three dogs surviving more than 60 days; however, four dogs not included in the above figures were still alive 100 to 286 days postoperatively at the time of this report. Neither pregnancy (204) nor antuitrin-S (204–206) had any preventive effect on ulcers produced in dogs with cinchophen. Also, the injection of histamine in beeswax is stated by Wangensteen (342) to produce ulcers in pregnant bitches, but no ulcers were observed in the fetuses.

Broad and Berman (341) confirmed the beneficial effect of A.P.L. extracts on Mann-Williamson dogs, finding that the average survival time of the treated animals was almost twice that of the control group. In further experiments, Sandweiss and his associates (340) made the following observations: (1) that increasing the dosage of A.P.L. hormone fivefold did not increase its prophylactic effect on M-W ulcers; (2) that

heating the preparation to the point of complete destruction of sex hormone activity did not alter its beneficial effect in M-W dogs; (3) that corpus luteum hormone did not affect the incidence of ulcer in a small series of animals; (4) that extracts of urine from normal nonpregnant women apparently had a prophylactic action against experimental ulcer, whereas (5) such activity was apparently absent from extracts of urine of patients with peptic ulcer. Friedman and Podolsky (435) showed that the anti-ulcer effect of urine extract was not due to prolactin. Subsequent investigations on urine extracts are discussed in relation to the gastrointestinal hormones (Chapter 13).

Comment. A number of significant observations have been made on the variations in the secretory activity of gastric pouches during various phases of the sexual cycle in female dogs. We (347) are in agreement with Klein (348), Hollander (349), and Winkelstein (350) that hypersecretion occurs during lactation and that it is frequently attended by extensive ulcerative processes of the abdominal wall about the stoma of the pouch. Winkelstein (350) found that theelin antagonizes and antuitrin-S aggravates this ulcerative tendency. Concerning the effect of estrus on these lesions of the abdominal wall and on gastric secretion, there is less unity of opinion. Klein (348) and Winkelstein (350) observed healing of peristomal lesions during estrus, although in Babkin's (351) experience and in ours (352), there is usually an augmentation of gastric secretion during estrus. There may be no essential relation between the hypersecretion and the erosive lesion; or, as Babkin (353) suggests, erosions of the abdominal wall may actually induce hypersecretion, which then would represent a result rather than a cause of the erosions.

The significance of these very important observations on the relation of the sex hormones to peptic ulcer is not yet clear. Although Sandweiss' investigations of pregnancy urine led ultimately to the discovery that there is a gastric inhibitory substance in the urine apparently unrelated to presently known sex hormones, his original avenue of research still holds considerable interest and promise, for no adequate explanation can be offered for the amelioration of peptic ulcer by pregnancy. The possible relationship of the marked rise in blood histaminase during pregnancy (551) deserves attention.

Production of Experimental Peptic Ulcer by Surgical Methods

Gastroenterostomy

In 1899, Braun (445) demonstrated the autopsy material from a case of perforated jejunal ulcer 11 months after gastrojejunostomy; this was

the first report of postoperative jejunal ulcer. Braun considered it possible that the mucosa may have been traumatized during the operation, and recommended gentle handling of the bowel to avoid this complication. Four years later, Watts (446) claimed to have produced the first postoperative jejunal ulcer in a dog; he listed the etiologic factors as (1) hyperacid gastric juice emptying directly into the jejunum, (2) injury to the mucosa of the intestine by foreign material or food particles, (3) interference with the circulation of the bowel at the time of operation, and (4) spasm of the jejunum from irritation by the gastric juice. Much experimental work has since been devoted to an investigation of the specific factor or factors involved.

Montgomery (447) made a study of gastroenterostomy in 60 dogs; in some of these animals, a hematoma was produced at the suture line, and in others, the suture line was inoculated with colon bacilli. Of the four cases of jejunal ulcer in this series, three developed at the site of a hematoma. No change in the incidence of ulcer was produced by the establishment of an enteroenterostomy between the afferent and efferent jejunal loops, by the use of nonabsorbable suture material, or by the use of clamps. Simple gastroenterostomy was reported by Brancati (448) in 28 dogs, with one instance of ulcer; by Hütten (449) and by Dogliotti and Riccio (450) in six dogs, with no ulcers; by Steinberg and Proffitt (451) in 30 dogs, with no ulcers; and by McMaster (452) in 11 dogs, with the production of jejunal ulcer in five. It must be mentioned that some of the investigators did not observe their dogs for a sufficiently long period of time after operation. Borszeky (453) fed two tablespoons of HCl daily to 12 dogs with gastroenterostomies and observed only one case of jejunal ulcer; the rest survived in good health for almost six months.



FIG. 64. Pyloric obstruction with gastrojejunostomy. The incidence of jejunal ulcer after this operation is high, but varies with the distance of the anastomosis below the pylorus.

Gastroenterostomy with interruption of the pylorus (section at or near the pyloric sphincter and closure of the stomach and duodenum) (Fig. 64) was followed by the development of jejunal ulcer in three of the 24 dogs reported by Baggio (454) and in 10 of the 20 dogs reported by DeBakey (455). In six dogs with this operation receiving 50 cc. of 1 per cent HCl for as long as 41 days, Exalto (456) did not observe any ulcers; the dogs were permitted to live up to 289 days.

We (41) connected the end of the stomach to the side of the duodenum with a large anastomotic orifice; the operation was performed without clamps in 30 dogs and no ulcers were observed in this series. In 40 other dogs, clamps were used in making the anastomosis, and in this group duodenal ulcer occurred in five dogs; the latter did not do well after the operation. Periti (457) reported superficial duodenal ulcers in two of three dogs after gastroduodenostomy with a large stoma.

Gussio (458) divided the stomach in half at about the middle, and in some dogs anastomosed the jejunum to the pyloric portion, in others to the cardial portion; only in the latter case did ulcers develop, indicating according to the author that acid was responsible for the lesions. DeHarven (459) could not confirm these results.

The high incidence of ulcer which followed the pyloric-exclusion operation introduced by Eiselsberg (547) stimulated considerable experimental inquiry into the cause of these ulcers; yet the data available indicate that this operation does not consistently lead to jejunal ulcer in the dog. For example, although Baggio (454) obtained ulcers in all of the four dogs, and Hutten in both of the two dogs that lived sufficiently long after the operation, the incidence reported by Ciminata (460) was three out of eight; by Brancati (448), one out of nine; and by Dogliotti and Riccio (450), none out of four. In spite of the claim that excision of the pyloric antrum prevents the development of ulcers which would occur if the antrum is excluded but not removed, experimental ulcer has been produced repeatedly by removal of the antrum and gastrojejunostomy (448, 460–462). As a matter of fact, the latter procedure has been suggested by Dott and Lim (461) as a method for producing ulcers consistently in the dog.

Some of the discrepancies in the foregoing reports are explainable, at least in part, on the basis of the work of McMaster (452) and of Wangensteen's group (436). McMaster (452) showed that the incidence of ulcer following gastroenterostomy increases as the anastomosis is moved distally in the intestinal tract; for example, there were no ulcers following gastroduodenostomy, whereas ulcers occurred in 100 per cent of the dogs surviving at least one week after gastroileostomy. The experiments of Merendino et al. (436) demonstrated that gastroenterostomy, even with extensive gastric resection, is followed by a high incidence of gastrojejunal ulcer if the afferent duodenojejunal loop is long; on the other hand, if the anastomosis is performed with the shortest possible afferent loop, stomal ulcers do not occur even if histamine-in-beeswax is administered. The significance of these and similar observations is dealt with in the subsequent discussion (p. 348).

Diversion of the Duodenal Secretions

In 1909, Bickel (463) excised the duodenum of a dog, performed a gastrojejunostomy, and attached the ampulla of Vater to the skin for the purpose of studying the factors concerned with the flow of bile and pancreatic juice. The animal died four and one half weeks later of peritonitis resulting from perforation of one of several jejunal ulcers. The author pointed out the significance of the unneutralized gastric juice as a cause of these ulcers, but he considered that this was not the only factor involved.

Two years later, Exalto (456) performed a gastrojejunostomy en-Y in four dogs, three of which developed jejunal ulcer. He then modified this operation so that the isolated duodenum, instead of emptying its secretions into the upper intestine, drained into the first part of the colon. When the three dogs in which this operation was performed developed jejunal ulcers, Exalto had become the first investigator to produce experimental ulcers by the method of internal duodenal drainage. His conclusions, valid now as then, were: (1) jejunal ulcer after gastroenterostomy results from the action of the acid gastric juice on the intestinal mucosa; (2) it remains to be established whether mucous membrane lesions must be present as a result of mechanical trauma or other primary reasons, or whether the chemical trauma suffices as a too highly acid medium for the survival of the mucosal cells. Thus, along with the operation for production of jejunal ulcers by duodenal drainage, there were introduced *the etiologic concepts of acidity, mechanical trauma, and mucosal susceptibility.*

Kehrer (464), in 1914, wished to investigate the role of pylorospasm and delayed gastric emptying in the etiology of ulcer. To produce these conditions experimentally, he ligated the common duct and anastomosed the gallbladder and pancreatic ducts to the appendix or ileum in 15 dogs (Fig. 65). Inanition developed in these animals, which survived from nine to 159 days; six had ulcerative lesions of the stomach, and one of these also showed ulceration of the duodenum. These lesions were considered by the author to be analagous to the early stages of human ulcer. In the same year, Langenskiold (465) obtained jejunal ulcerations by draining the duodenal secretions into the upper intestine in one dog.

In 1921, Denk (466) performed the following operation in two dogs: the pyloric sphincter was excised, and the duodenum and stomach closed with purse string sutures; the jejunum was sectioned 25 cm. distal to the pylorus, and the proximal end of the cut jejunum anastomosed to the side of the terminal ileum; the distal end of the jejunum was purse-stringed and the continuity of the digestive tract reestablished by a side to side anastomosis of the stomach to the jejunum. One of the dogs died 11 days after operation with no sign of ulcer; the other was sacrificed after

six weeks and had two jejunal ulcers, one of which had perforated. Two years later, Mann and Williamson (467) performed the same operation, except that an end to end anastomosis was made between the stomach and jejunum (Fig. 66). These investigators observed a large number of dogs and made a thorough study of the origin and evolution of the lesions, with the result that the operation of duodenal drainage has come to be designated by their names. It will be so designated in this discussion, and abbreviated "M-W."

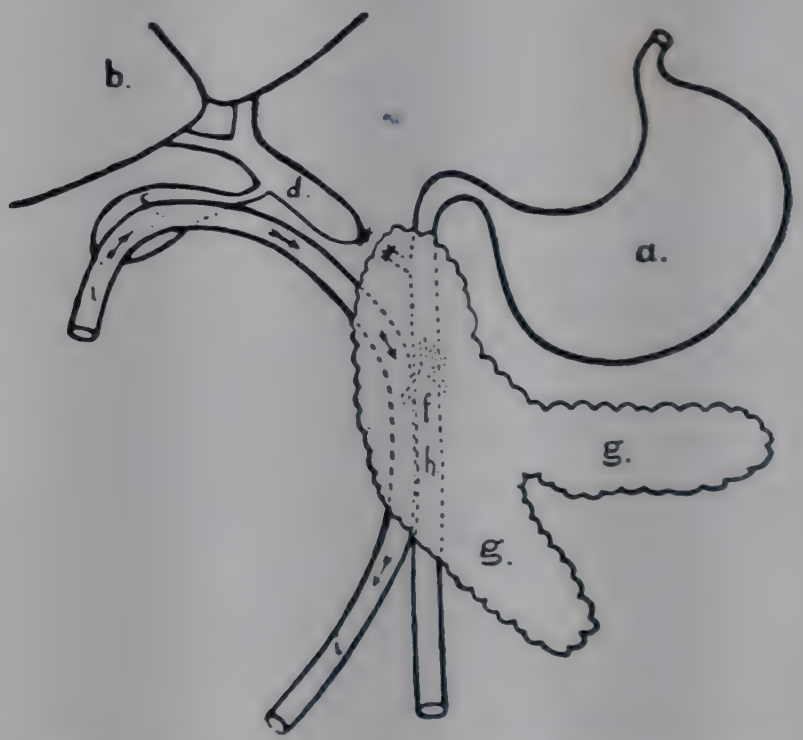
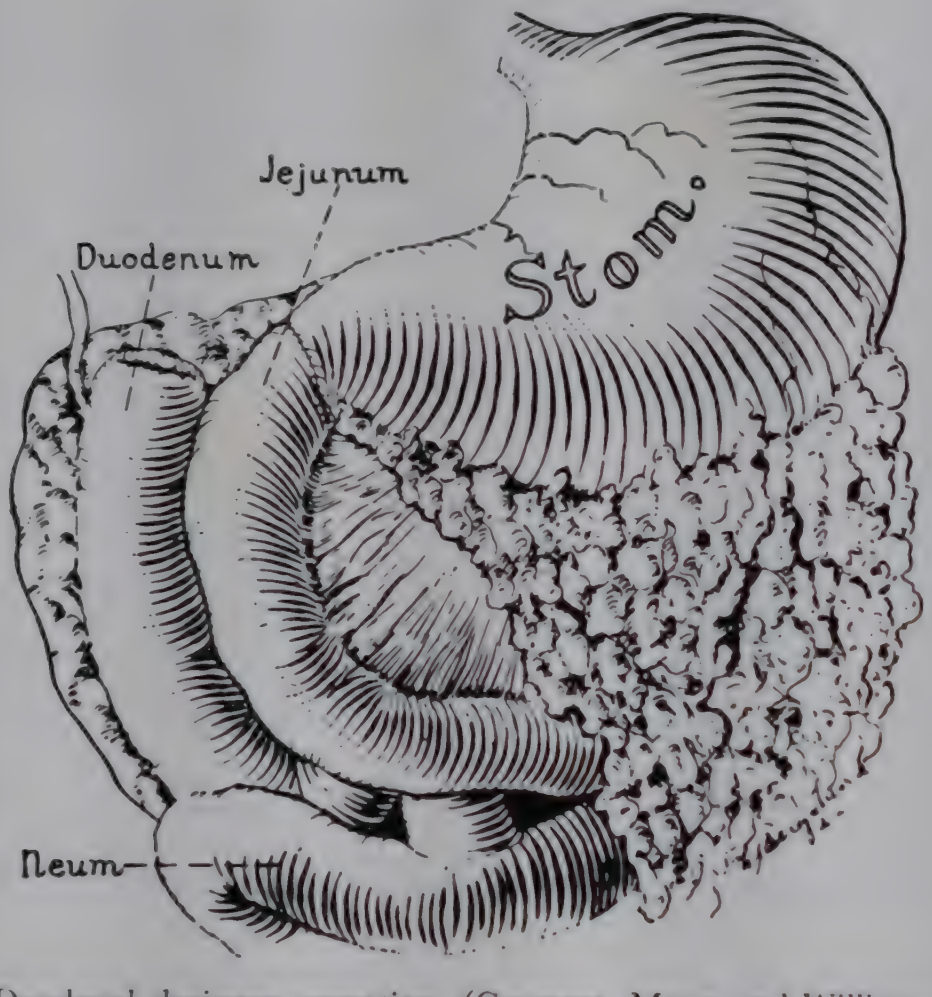


FIG. 65. Diversion of bile and pancreatic juice. *a*, stomach; *b*, liver; *c*, gallbladder; *d*, common bile duct; *f*, lesser pancreatic duct; *g*, pancreas; *h*, duodenum; *i*, loop of ileum. (Courtesy, Kehrer: *Mitt. a. d. Grenzgeb. d. Med. u Chir.*, **27:** 679, 1914.)

In their classic report, Mann and Williamson (467) presented observations on 16 dogs in which the duodenal secretions emptied into the terminal ileum from 25 to 75 cm. proximal to the cecum; 14 of these dogs developed jejunal ulcers. Of 10 dogs in which the duodenum was resected and the bile and pancreatic ducts anastomosed to the terminal ileum, eight developed jejunal ulcers in 12 to 124 days. The characteristics of jejunal ulcers produced by diverting duodenal secretions to the lower intestine have been outlined by Mann (468) as follows: (1) Peptic ulcer develops in almost 100 per cent of the dogs operated upon. (2) The time of ulcer formation varies; perforation may occur in 10 days, or ulcer may not start to develop until three months after operation. (3) Although the animals lose weight, the change in general physical condition does not



IG. 66. Duodenal drainage operation. (Courtesy, Mann and Williamson: *Ann. Surg.*, 77: 409, 1923.)

ppear to be a primary factor. (4) Operative trauma is not a factor. 5) Impairment of blood supply is not a factor. (6) The ulcer is always und in the intestinal mucosa just distal to the suture line, lateral and osterior to the central axis of the intestine. However, the site of the ulcer ay be changed by rotating the loop of jejunum anastomosed to the omach; i.e., it bears a constant relation to the point of emission of the istric chyme. (7) The ulcers are usually single. (8) Grossly and microopically, the ulcer appears similar to the postoperative jejunal ulcer of an. (9) The ulcer heals readily if protected from the gastric content. orton (469) reported that the jejunal ulcers in M-W dogs could be monstrated by x-ray following a barium meal; there was no change in e gastric motility after the operation, but with the formation of ulcer e emptying time was delayed. The author ascribed this to jejunal spasm sulting from irritation at the site of the ulcer.

With regard to general changes occurring in dogs after duodenal ainage, Flood and Mullins (470) reported that there was a progressive op in the total blood protein, involving chiefly the albumin fraction, me decrease in the blood amino nitrogen, secondary anemia, degenera-

tive changes in the liver, kidney, and other organs, decreased serum bicarbonate, a fall in the blood cholesterol, and an alteration of the serum electrolyte pattern. These findings were essentially confirmed by Martinez and Chamorro (471) in studies on dogs with the duodenal secretions drained to the exterior. Reymont (191) indicated that prior to the development of ulcer the liver function in M-W dogs was not detectably impaired, as judged by the quantitative bilirubin test and the blood lipase and bromsulphthalein retention determinations.

We (472) found that there is no correlation between the postoperative fall in blood alkaline reserve and the rate of development of the ulcer in M-W dogs. In our experience, anemia does not usually appear until the ulcer starts to bleed. By weighing these dogs and making hemoglobin determinations on them at regular intervals postoperatively, we (473) observed that the anemia was not a result of the nutritional disturbance. Shoch and Fogelson (437) observed the onset of anemia and a fall in total protein and in the albumin-globulin ratio after the development of the ulcer. Fig. 67 shows the time of survival and the time of onset of the ulcer in a series of 42 M-W dogs. It is apparent from this graph that a diagnosis of ulcer was made in 90 per cent of the animals within nine weeks after operation, and that the ulcers developed in most dogs between the fourth

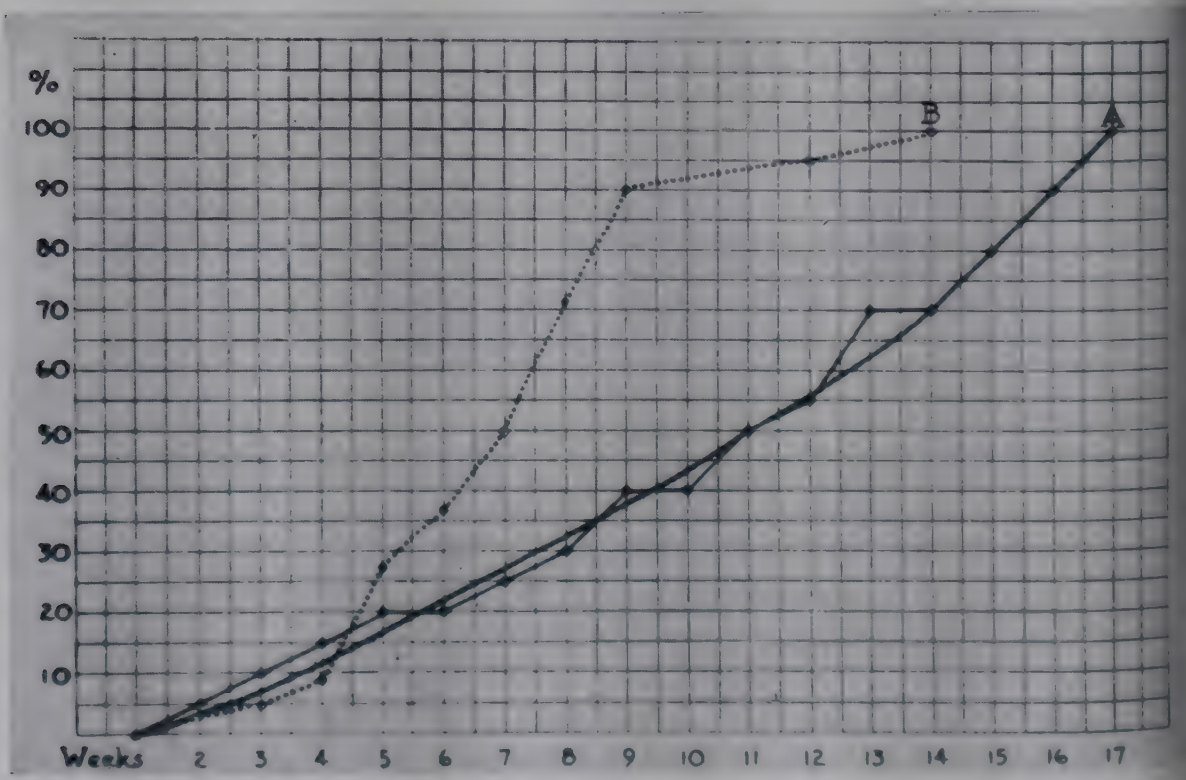


FIG. 67. Curve A represents the percentage survival time of 42 untreated control dogs. Curve B represents the percentage diagnosis-time of ulcer in 22 of the dogs; for example, 50 per cent of the dogs had ulcer at 7 weeks. (Courtesy, Orndorff, Fauley and Ivy: *Am. J. Digest. Dis.*, **3**: 26, 1936.)

nd ninth weeks. On the basis of these observations, we do not attach any ignificance to any reports of successful ulcer-preventive measures in M-W logs if the animals do not survive at least two months without ulcers. *It s very important to keep in mind that M-W dogs may die of complications before hey have lived long enough to develop ulcer*, and that an occasional M-W dog nay go on indefinitely without developing an ulcer.

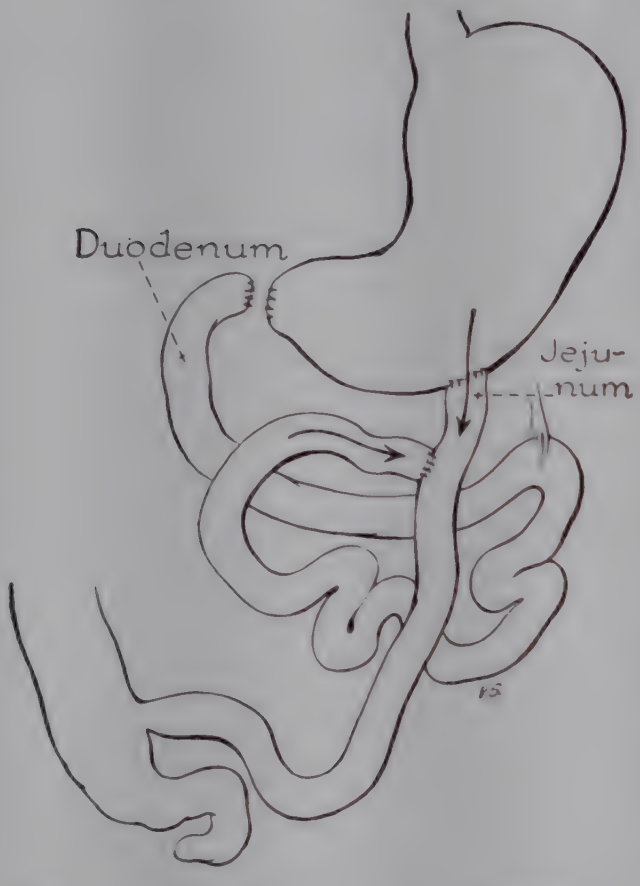


FIG. 68. Modification of Mann-Williamson operation as performed by de Harven. (Redrawn from *Arch. internat. de méd. expér.*, **2:** 326, 1925–26.)

The experiments of Mann and Williamson have been confirmed in ery report published on the subject except that of de Harven (459), no modified the operation so that the duodenal branch was very long ig. 68); moreover, his series consisted of only two dogs surviving only and 25 days respectively. It was stated by a group of investigators 74) that ulcers following duodenal drainage occur not only in e jejunum, but also in the excluded duodenum and in the ileum. ne authors were surprised, in view of the enormous number of animals died by previous workers (Table 14), that no one had ever called ention to these duodenal and ileal ulcers. But the "ulcers" referred to re mucosal depressions overlying lymph follicles, and erosions (see apter 1).

Etiology of Postoperative Jejunal Ulcer

The Factor of Nutrition. The marked loss of weight which occurs in M-W dogs focuses attention on the relation of malnutrition to the ulcers which develop following duodenal drainage. Mann (475) considered it proven, by exploratory operations and by a study of symptoms, that the sudden decrease in weight does not occur until the ulcer has formed, and Morton (476) stated that the loss of weight seemed a result, rather than a cause, of the ulcer. Yet it is difficult to accept these statements in view of the obvious impairment to digestion and absorption suffered by dogs in which the bile and pancreatic juice are acting only in the terminal portion of the intestine. One would expect, under such

Table 14

Incidence of Jejunal Ulcer in Dogs Following Internal Duodenal Drainage (Untreated Animals)

Observers	*No. Dogs*	*No. with Ulcers*	*Observation Period*
Exalto (1911) (456)	3	3	21–37 da.
Denk (1921) (466)	2	1	3–6 wk.
Mann & Williamson (1923) (467)	16	14	Not given
Morton (1927) (469)	20	20	14 da.–4 mo.
Morton (1927) (519)	9	9	20–65 da.
Fauley & Ivy (1929) (157)	4	4	2 mo.
Scott (1929) (537)	8	6	4–10 wk.
Weiss & Hubster (1929) (158)	17	17	12–45 da.
Neuman, de Moor, Deloyers (1930) (159)	6	4	12 da.–2 mo.
Weiss & Gurriaran (1930) (162)	15	15	12 da.–2 mo.
Jenkins & Palmer (1930–31)* (480)	10	9	32–228 da.
Giaccobe & Vitale (1931) (163)	6	6	8–52 da.
Beaver & Mann (1931) (504)	3	3	Not given
Paolucci (1931) (165)	10	10	20–45 da.
Owings & Smith (1931–32)* (482)	26	10*	42–428 da.
Steinberg & Proffitt (1932)* (451)	14	12*	4–90 da.
Caraco (1932) (169)	3	3	12–48 da.
Gallagher & Palmer (1932–33)* (481)	47	38*	14–619 da.
Manfredi (1933) (479)	6	6	15–137 da.
Weiss & Aron (1933) (484)	2	2	3–5 wk.
de Oliveira & Strazzacappa (1934) (170)	2	2	37–91 da.
Cerqua (1936) (487)	36	32	4–7 wk.
Orndorff, Fauley, Ivy (1936) (472)	42	42	14–120 da.
Flood & Mullins (1936) (470)	5	5	51–104 da.
Sandweiss, Saltzstein, Glazer (1937) (544)	12	12	16 wk.
Shoch & Fogelson (1942) (437)	10	8	24–340 da.

* Drainage point varied.

ircumstances, that the loss of weight which immediately follows the peration would continue until the animals' death; in other words, the nimals are almost certainly losing weight when the ulcer develops. This as clearly shown in our (472) data based on a series of 42 M-W dogs. he average weight loss in these dogs from shortly after operation until eath was 31 per cent; 84 per cent of this loss had occurred by the time a iagnosis of ulcer was made; 45 per cent was lost in the first 17 days, or 5 days before the average time of development of ulcer and seven days efore the earliest diagnosis of ulcer in the entire group. Almost identical gures were obtained by Slive and his co-workers (477) in a series of 6 dogs.

These observations raised the question whether the loss of weight was oncerned in the development of the ulcers. Experimental inquiry into is question has consisted of (1) alteration in the level of duodenal rainage, (2) production of nutritional disturbance without duodenal rainage, and (3) attempts to identify some specific nutritional deficiency M-W dogs.

Alteration in the Level of Duodenal Drainage. The objective of this method to empty the bile and pancreatic juice into the intestine at a level where fficient digestion will take place to maintain the animals' weight, yet r enough distal to the gastrojejunostomy to prevent neutralization of e gastric juice. (In all of our work on M-W dogs, the duodenal secretions e drained into the ileum 15 cm. proximal to the ileocecal junction.)

Neuman, de Moor and Deloyers (478) anastomosed the isolated duo- num to the intestine from 80 to 100 cm. proximal to the cecum; of four gs, two lost weight and developed ulcer, while the other two remained rmal. Nevertheless, the authors considered that malnutrition was not a termining factor in the appearance of ulcers in M-W dogs. Manfredi 79), on the basis of identical results, reached a diametrically opposite nclusion.

Jenkins and Palmer (480) and Gallagher and Palmer (481), who served large series of dogs in which the drainage point was varied from ar the gastrojejunostomy to near the cecum, concluded that the level of ainage did not alter the incidence of ulcer, but that the dogs with more oximal implantation of the duodenum survived longer.

Owings and Smith (482) and Steinberg and Proffitt (451) anastomosed duodenum to the intestine 60 cm. distal to the gastrojejunal stoma. e former obtained ulcers in 10 of 26 dogs in an average time of 118 s; the remaining 16 dogs died of "extraneous causes" without ulcer an average of 26 days. The latter investigators obtained ulcer in all of en dogs; in five of these the ulcer had perforated between the 5th and h postoperative days. These comparative figures illustrate how con-

ditions vary in different parts of the country. Slive et al. reported 50 per cent ulcers in dogs in which the duodenum was drained approximately midway in the small intestine; all of the animals which developed ulcer showed a loss of weight, and in none of those which gained weight did ulcers occur. A second operation was performed on the surviving dogs, effecting a reduction of the distance between the duodenal drainage point and the ileocecal sphincter to 40 cm. Thus, all factors were kept the same except for the reduction in the nutrition. The dogs then proceeded to lose weight and develop ulcers.

Surgical Production of Nutritional Disturbance. McMaster (483) reported observations on a series of 20 dogs in which the first part of the jejunum was sectioned, the distal end closed, and the proximal end anastomosed to the colon. Thirteen of these dogs developed prepyloric or duodenal ulcers; the survival time was 50 days or less in all but one animal. In another series of 11 dogs, the excluded small intestine was resected and only two dogs developed ulcers. This suggested to the author that the intestine might play some role in ulcer causation. Deloyers (192) repeated the first of these experiments, except that the jejunum was anastomosed to the terminal ileum (Fig. 69). Thirteen dogs survived from 17 to 118 days; the degree of malnutrition was similar to that observed in M-W dogs, yet only one dog developed duodenal ulcer. This was confirmed by Slive and his associates (477).

Specific Deficiency. Although we (472) and Fogelson (437) were able to delay the onset of ulcers in M-W dogs by feeding large amounts of a highly nutritious diet with raw ground pancreas and liver, Weiss and

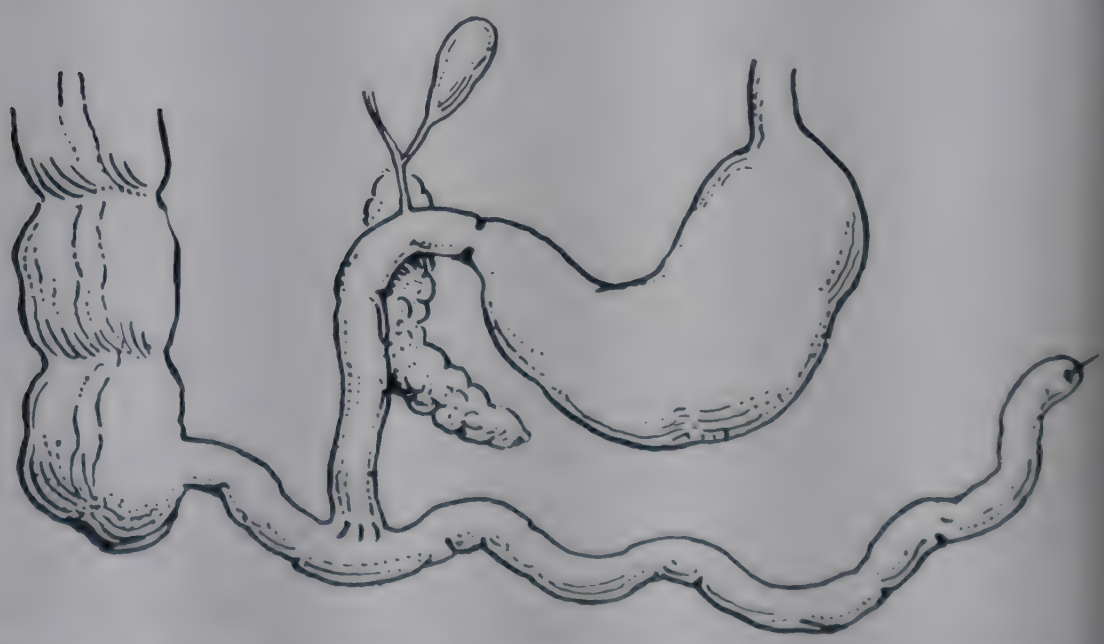


FIG. 69. Short-circuiting operation of Deloyers. (*Courtesy, Arch. internat. de méd. expér.*, **11:** 1, 1936.)

Aron (484) were unsuccessful in similar attempts. The latter authors herefore concluded that

> deficiency of substances indispensable to life, furnished by the food and not synthezable by the organism, is the basis of ulcer causation. Since the digestion of protein rendered impossible by duodenal drainage, the causal factor can only be certain mino acids, terminal and assimilable products of digestion.

This concept was tested in M-W dogs by feeding the amino acids tryptophane, lysine, and histidine; these experiments, as well as the line of easoning upon which they were founded, are treated in some detail as an llustration of the manner in which clinical therapeutics may be influenced y the most tenuous conclusions from animal experiments.

The first group of animals studied by Weiss and Aron consisted of six ogs; two served as controls and died with ulcers three and five weeks espectively after the operation. The remaining four were injected subcuaneously with a solution containing 0.05 Gm. of histidine and 0.025 Gm. f tryptophane daily; in these dogs, there was only a moderate cachexia nd the stools never contained blood. Two of the dogs were sacrificed at he end of three weeks, one at six weeks, and the remaining one at 10 eeks, and in no case was there any trace of gastric or jejunal inflammaon or ulcer. The authors then prepared a second group of five dogs, two which received daily an unstated amount of 2 per cent tryptophane, he an unstated amount of 4 per cent lysine, and the last two received cc. of 4 per cent histidine. The first three dogs followed a course identical ith that of the controls, so that no beneficial action could be ascribed to ther tryptophane or lysine. But the two dogs receiving histidine had a fferent course; one was put to death in good health eight weeks postperatively, with an entirely normal digestive tract, while the other

> d a very curious history . . . he was in excellent condition eight weeks after operan, without traces of blood in the stools. Because of an oversight by the diener, four ys elapsed without giving him the histidine. He died the fourth day and we found autopsy a minute perforation, large as the head of a pin. . . . This perforation in way resembled the usual experimental ulcers. We think it evolved from the day en the animal no longer received histidine.

Thus, when the evidence is examined, we discovered that the clinical plication of histidine in the treatment of peptic ulcer rests on one M-W g surviving eight weeks without ulcer after daily injections of histidine. iss and Aron went on to state:

> have other confirming experiences underway, but for the present we are permitted elieve that histidine, by a specific action, is capable of preventing the evolution of erimental ulcer by duodenal drainage.

Further confirmatory experiments from these authors have not, how ever, come to our attention.

This work is to be contrasted with the careful experiments of Shoc and Fogelson (437). Their 10 control M-W dogs on a casein diet survive an average of 131 days; by feeding a casein hydrolysate, presumably con taining all of the animo acids, the authors were able to double the surviva time of their dogs, and to delay but not prevent the development c ulcers. One of the most significant observations made in this study wa that ulcers developed in the amino acid fed dogs while the animals wer still in a relatively good state of nutrition; this indicates that malnutritio is not an *essential* factor in the etiology of postoperative jejunal ulcer.

Fontes and Bauer (485) prepared a series of dogs by feeding them a di sufficiently high in protein to guarantee the ingestion of at least one gra of histidine daily. After a preparation period of from seven to 39 day the M-W operation was performed on these animals, which were the given 0.25 to 0.5 Gm. of free histidine daily. Of the seven dogs survivin longer than 10 days, two died without ulcer; it is interesting to note th three dogs in this series had prepyloric ulcers, a very rare occurrence i M-W dogs.

Flood and Mullins (470) were able to prevent or to delay the onset ulceration in 45 per cent of 12 M-W dogs receiving 4.8 to 10.9 mg. p kilo of histidine hydrochloride, and Toro (486) found that daily injectio of 2.5 cc. of a mixture of 4 per cent histidine and 2 per cent tryptopha gave complete protection from ulcer to five M-W dogs. Toro did n bother with control experiments because he considered it was we established that ulcer invariably occurs, without respect to time, followi duodenal drainage.

In order to repeat the experiments of Weiss and Aron properl Cerqua (487) followed their technique identically with respect to oper tion, pre- and post-operative care, and dose and route of administrati of histidine; he was unable to detect any difference between histidin treated dogs and controls. Similar results were obtained by Fogels (439), by Sandweiss et al. (544), and by Wu (488). Barry and Florey (48 administered histidine to cats and pigs with experimental Mecke diverticula and found no protective value in the drug.

The advocates of histidine believe that it specifically protects t gastrojejunal mucosa from ulceration. That it does not reduce the gast acidity in dogs has been established (433, 490). Jacob (491) believe however, that since histidine is converted to histamine in the gut, it m be the latter substance which is responsible for the protective actio Accordingly, he administered $\frac{1}{15}$ to $\frac{1}{10}$ mg. of histamine (the amou theoretically derivable from one ampule of commercial histidine) to fo

M-W dogs; the survival periods were 11, 12, 33, and 42 days respectively, nd none of the animals developed ulcers. This was confirmed clinically n three ulcer patients. Such work has no scientific significance.

Comment. A thorough investigation of all aspects of the relation of malnutrition to experimental postoperative jejunal ulcer has been made by Fogelson (439, 477). Some of his observations led him to believe that f it were possible to keep M-W dogs from losing weight, the development of ulcer might be postponed indefinitely. The most potent argument gainst Fogelson's view is this: that if the gastrojejunal anastomosis is taken lown after the jejunal ulcer has developed in a M-W dog, and another gastrojejunostomy is performed more distally in the intestine, *the original lcer will heal while a second ulcer forms at the new anastomosis.* Thus, if an ulcer will heal in the face of impaired nutrition, the latter can hardly be an ndispensable factor in the genesis of the lesion.

The predominating trend of evidence indicates that when the nutrition f M-W dogs is maintained by draining the duodenal contents at a higher evel in the intestine, the incidence of ulcer is materially decreased. This nethod, unless well-controlled by repeated gastric analyses, has the isadvantage that as the site of drainage approaches the gastroenterostomy, he factor of neutralization comes in. Improvement of nutrition by special ttention to diet delays, but does not prevent, the occurrence of ulcers.

Short-circuiting the small intestine to produce a degree of malnutri- on comparable to that in M-W dogs occasionally results in the formation a duodenal ulcer.

The contention that histidine supplies a specific protection against lcer in M-W dogs cannot withstand critical inspection of the experimental vidence.

The Factor of Acidity. It has been stated by many investigators that cers which follow the diversion of the biliary and pancreatic secretions e due primarily to the corrosive action of undiluted and unneutralized stric juice on the intestinal mucosa. Mann (475) has stated, for example, at there is no doubt that the visible signs of the beginning of the ulcer e due to the acid. Several types of experiments have been devised in an tempt to procure convincing evidence on this point.

Experimental Meckel's Diverticulum. One might say that the first experi- ent in which the intestinal mucosa was exposed to the action of pure stric juice was performed by Nature, inasmuch as acid-secreting tissue occasionally found in a Meckel's diverticulum. Winkelbauer (492), in 26, attempted to reproduce this condition by anastomosing a Pavlov uch to the intestine at various levels—to the duodenum in one dog, to jejunum in two dogs, and to the ileum in five dogs. Only three of the imals lived a significant length of time (32, 108, and 134 days), and

none of them developed ulcers; one dog, which died twelve days after operation, had a small lesion in the ileum adjacent to the gastric pouch, but the author considered this unimportant and concluded that bringing acid into contact with the lower ileum does not cause ulcers. In similar experiments conducted by Matthews (493), the operation was modified so that the ileum receiving the gastric contents was kept relatively free from food material (Fig. 70); large, chronic ileal ulcers were found from

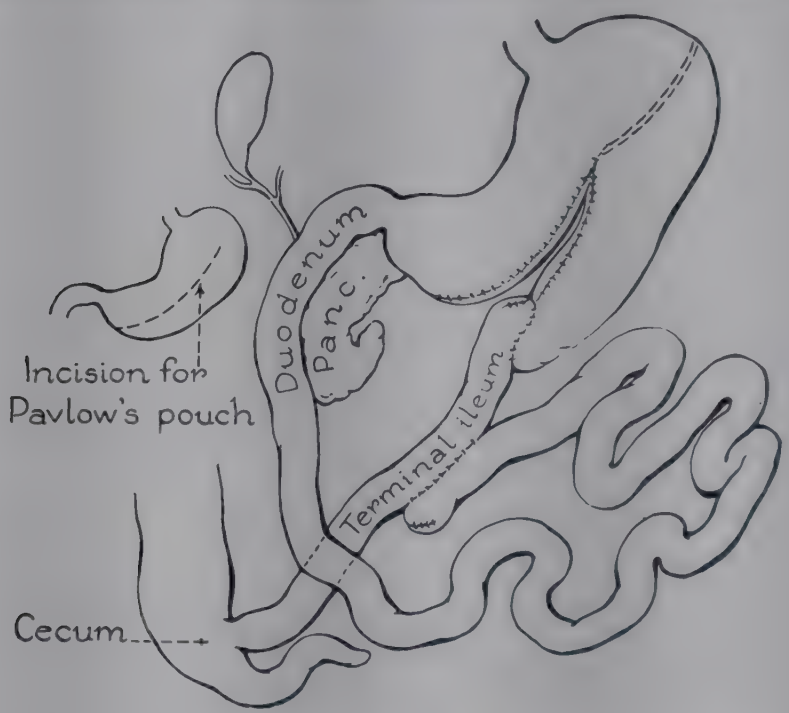


FIG. 70. Operation for the experimental production of "Meckel's diverticulum ulcer." (Redrawn from Matthews and Dragstedt: *Surg., Gynec. & Obst.*, **55:** 265, 1932.)

30 to 80 days after the operation in all six dogs on which the procedure was carried out. The author emphasized the fact that these animals were in good health and in a good state of nutrition, so that the lesions must be ascribed to the action of the gastric juice. Matthews' operation was employed by Barry and Florey (489) in cats and pigs, with the production of chronic ulcers in 100 per cent of the cases.

Wu and Thompson (494) fashioned a tube from the fundus of the stomach and spliced this into the ileum in seven dogs; ulcers of the intestine formed and perforated very rapidly in two of the dogs. In the remaining five, a part of the intestine was short-circuited to prevent food from passing through the transplanted pouch; of the four dogs surviving this operation, one developed an ileal ulcer which perforated into the stomach. In the remaining three dogs, the duodenum was isolated and anastomosed to the terminal ileum; two of these animals developed ileal ulcers adjacent to the gastric transplant, and one had a jejunal ulcer.

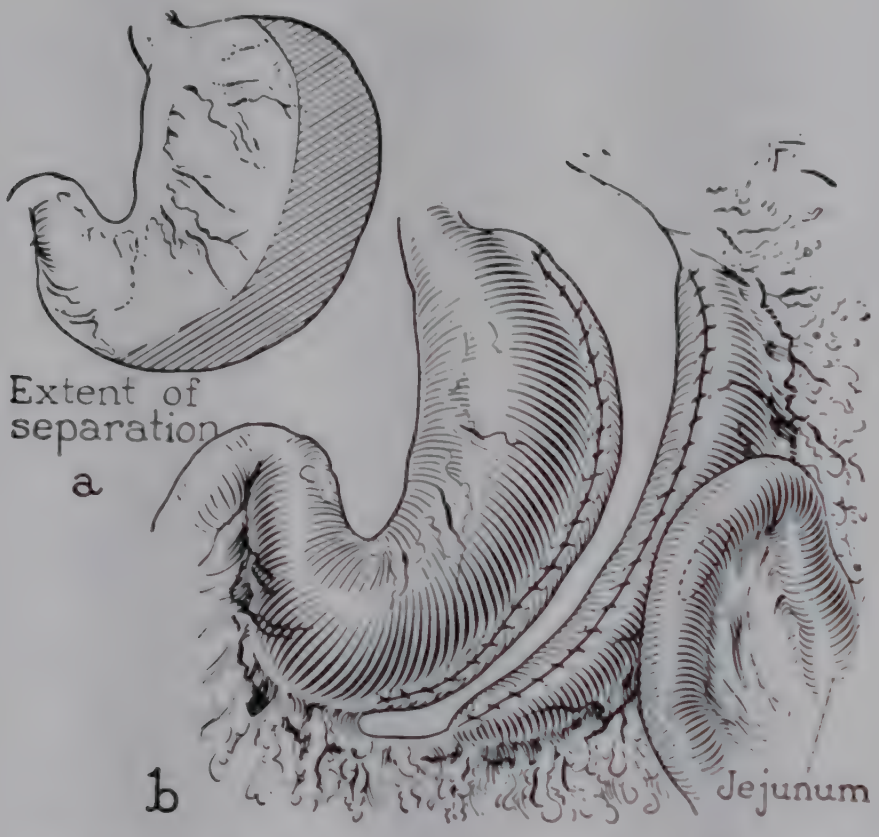


FIG. 71. The drawing in the upper left-hand corner (*a*) shows the extent of section of the region of the greater curvature or the amount of the stomach to be incorporated into a gastric pouch. The larger drawing (*b*) illustrates the formation of a pouch from the greater curvature, with a side-to-side anastomosis of a loop of the proximal jejunum to this pouch. (Courtesy, Gage et al.: *Arch. Surg.*, **10:** 19, 1936.)

These experiments confirm the previous findings that ulcers will develop in the intestine adjacent to an experimental Meckel's diverticulum.

Gage, Ochsner, and Hosoi (495) reported that when a pouch of the greater curvature was anastomosed to the jejunum (Fig. 71), ulcers developed in 100 per cent of the dogs, whereas the incidence was only 5 per cent when the jejunum was made to receive the secretion from a pouch of the lesser curvature (Fig. 72).

A method described by Goldberg and Mann (496) for preparing pouches of the fundus of the stomach turned out to be a good method for producing intestinal ulcers by the action of pure gastric juice. The first stage of the procedure consists of connecting a short ileal loop antiperistaltically from the skin to the fundus; in the second stage, the fundus is inverted into a pouch. The authors stated that during several months of observation they did not see any leakage from these fistulas, "thus passing the question of absorption of the acid by either the stomach or more probably the ileal mucosa."

Later, however, Goldberg (497) reported that ulcers developed frequently in these fistulas, and Harper (498) used such preparations to

study the development and treatment of peptic ulcer. Harper made the observation that when the pouch was constructed in the cardiac or in the pyloric region, no ulcers occurred in the fistula, and when two intestinal fistulas were made into the same fundic pouch, no ulcers occurred in either fistula until one of them was removed. Furthermore, in contrast to the observations of Matthews, it was noted that when ulcers were forming, the dog's general condition was poor; that is, there was anorexia,

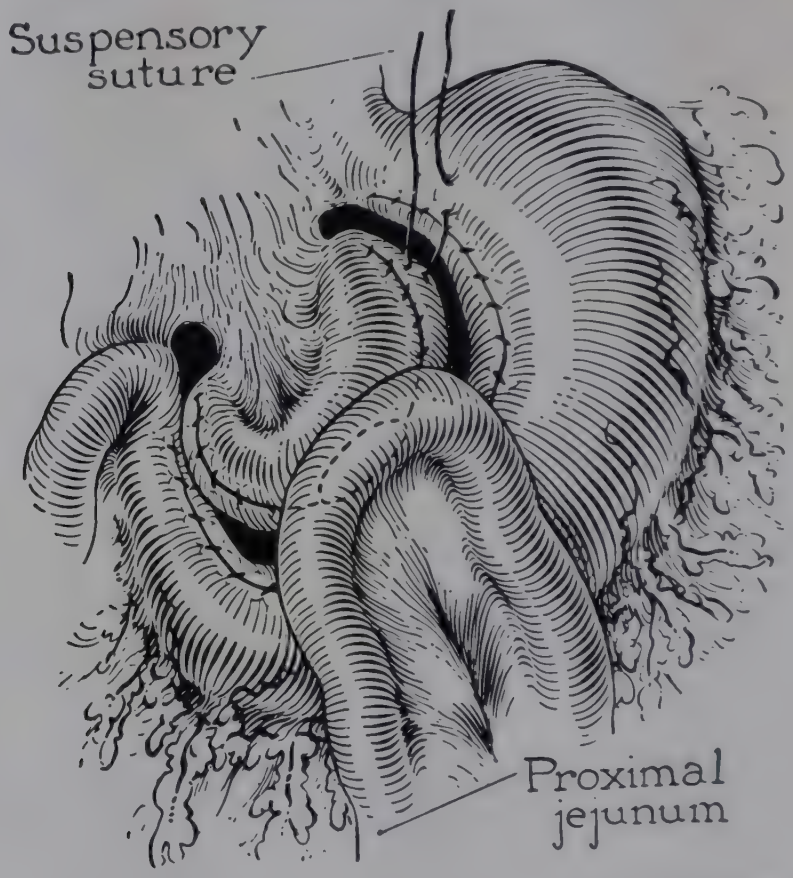
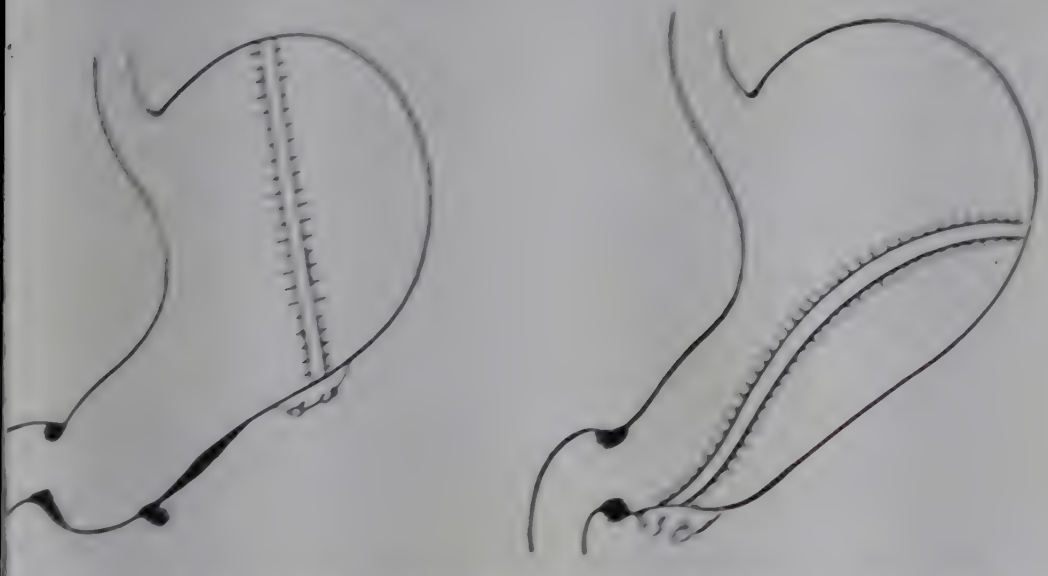


FIG. 72. A drawing showing the formation of a gastric pouch from the lesser curvature and anastomosis of a loop of the proximal jejunum. Note the suspensory suture to prevent the pouch from being pulled or stretched subsequently. (Courtesy, Gage et al.: *Arch. Surg.*, **10:** 10, 1936.)

vomiting, and loss of weight. The same finding was reported for pigs by Florey et al. (499). Harper's findings were confirmed by Kunlin and Cavalli (500). Palma (501), on the basis of nine experiments lasting up to 155 days, denied that fistulae into the fundus resulted in ulcers; he obtained ulcers of the intestinal segment in 77 per cent of his animals when the fistula was made in the pyloric antrum. This cannot, however, be construed as a contradiction of Harper, because Palma was not working with pouches.

Commenting on the relative infrequency of ulceration in Pavlov



Fundic-pyloric pouch. (Courtesy, Orator: *Zentralbl. f. Chir.*, **59**: 2389, 1932.)

s, Orator (502) suggested that it was because of the presence of ndic mucosa, which rarely ulcerates in humans. Therefore, he cted a "fundic-pyloric pouch" (Fig. 73) in seven dogs, two of eveloped pyloric ulcers while in good condition. At the same time, dt (79) observed that ulcers occur in the vagally innervated pouch ntire stomach, and even in a large Pavlov pouch if the latter is so cted as to interfere with free drainage of the gastric secretion). (The metal cannula used in Dragstedt's experiments must be red as a predisposing factor.) Ulcers do not, in our experience, in vagally denervated pouches of the entire stomach if the gastric constantly drained away.

s, it has been demonstrated that gastric juice *per se* is capable of ng postoperative jejunal ulcer. If gastric juice is an essential factor ppearance of postoperative jejunal ulcer, it should be possible to the lesion by (1) reducing or eliminating the free acid in M-W d (2) altering the level of duodenal drainage so as to permit some of intermingling of the duodenal secretions with the gastric as they leave the stomach.

ol of the Acidity in Mann-Williamson Dogs: Surgical Methods. (476) reported that when duodenal drainage was instituted after of the distal third of the stomach, the jejunal ulcers resulting ually acute or subacute, but Matthews and Dragstedt (79) ob- o reduction in the frequency or severity of jejunal ulcer in M-W the pyloric antrum removed (Fig. 74). In the hands of Stalnberg ffitt (451), subtotal gastric resection reduced the incidence of m 100 per cent to 10 per cent in M-W dogs, although the authors

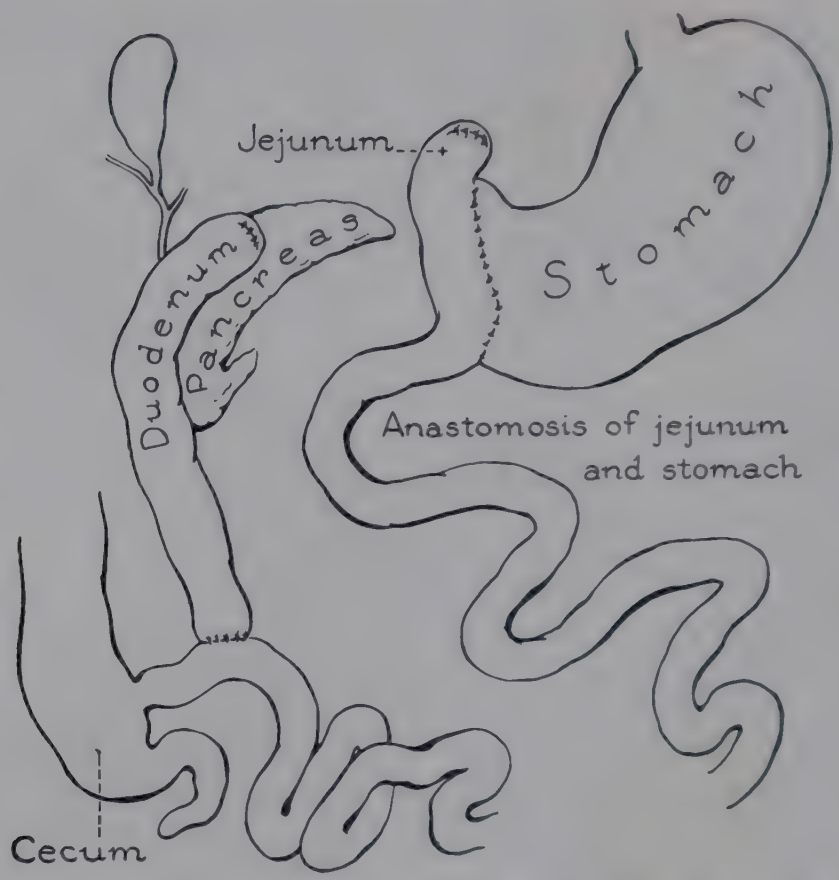


FIG. 74. Mann-Williamson operation with resection of pyloric antrum an large anastomosis. (Redrawn from Matthews and Dragstedt: *Surg., Gynec. & Obst* **55:** 265, 1932.)

did not ascribe this result to a reduction in gastric secretion. With th operation shown in Fig. 75, Deloyers (192) did not observe jejunal ulc in four M-W dogs surviving only up to 34 days; this confirmed the findin of Constant (319).

We (503) demonstrated that when most of the acid-secreting tissue the stomach was removed (Fig. 76), and a M-W operation then pe formed, the incidence of ulcer was reduced from 100 per cent to 27 p cent in dogs on a stock diet, and from 60 per cent to zero in dogs on special diet and observed from one to two years. In the fundusectomize animals, the average volume of gastric contents four hours after a me was about half that of the control M-W dogs. Also, the fundusectomize dogs secreted less to histamine. These experiments were interpreted conclusive evidence that acidity is the prime factor in the etiology postoperative jejunal ulcer. Resection of the fundus was reported Zilocchi and Calvi (440) to protect against ulcer in M-W dogs wi duodenal drainage high in the jejunum only when the gastric acidity w significantly reduced as determined by periodic gastric analyses. The same investigators observed the disappearance of the ulcer in one instan in which fundic resection was performed after the ulcer had developed.



FIG. 75. Gastric resection with duodenal drainage. Delovers' dogs did not ve long enough to permit definite conclusions to be drawn. (Courtesy, Delovers: *rch. internat. de méd. expér.*, **11:** 2, 1936.)

According to Hey (367), ligation of the vessels on the lesser curvature the stomach prevented the formation of ulcer in five M-W dogs examined from six weeks to 22 months after operation. In five other M-W ogs, the ulcer was permitted to develop; then the gastric ligation was rformed. Complete healing occurred in four dogs; the remaining dog, hich originally had two ulcers, died 27 days after the operation. One cer was found healed; the other showed evidence of healing. The author plies that the arterial ligation owes its beneficial effects partly to duction of gastric secretion and partly to cutting of a portion of the stric nerve supply along with the vessels. But according to Beaver and ann (504), no preventive effect against M-W ulcers was observed in ree dogs in which the adventitia of the celiac vessels was stripped completely. In three other M-W dogs, a transthoracic bilateral vagotomy was rformed; two of the animals died with ulcers, while the fate of the third the length of its survival are not mentioned by the authors. Saltzstein al. (546) reported the development of ulcer in six of eight vagotomized -W dogs surviving more than one month. Attention was called to the currence of a jejunitis of varying severity in 60 per cent of the vagotnized animals, a complication which was never so marked or so frent in the controls.

We (556) found vagotomy to provide no protection against ulcer in -W dogs and Oliver (172) also came to this conclusion. Harkins and

Hooker (550), on the other hand, reported almost complete protection against M-W ulcers by vagotomy, and no mention was made of jejunitis.

Medical Control of Acidity: Comparatively little work has been done on the control of gastric acidity in M-W dogs by nonsurgical means, perhaps because of the great amount of attention which the animals require in such experiments. Harper (498), in a study of the ulcers developing in ileal fistulas into a fundic pouch, reported that sodium bicarbonate



FIG. 76. Shaded area shows approximately the amount of fundus removed in performing fundusectomy for prevention of Mann-Williamson ulcer. (Courtesy, Fauley and Ivy: *Surg., Gynec. & Obst.*, **63:** 717, 1936.)

depressed the acidity temporarily, that mucin stimulated secretion, and that the formation of ulcers in the intestine could be prevented by the application of a special preparation consisting of gelatin, acacia, water and olive oil. Meyer and Rubin (505) were unable to cure ulcers in M-W dogs by the administration of alkalis, but we found that the administration of alkalis at frequent intervals prolonged the average survival time about two weeks; mucin therapy delayed the onset of ulcer in some dogs and occasionally prevented the occurrence of ulcer. Healing of jejunal ulcers was obtained in seven of eight dogs when mucin was instituted as soon as the ulcer appeared and the ulcers invariably recurred when mucin therapy was withdrawn, but it was almost impossible to obtain healing if the ulcer was permitted to progress for some time. We did not determine the acidity in these dogs; however, the gastric emptying time was somewhat reduced by both mucin and alkalies. Rodino (506) con-

tect no beneficial effect from the feeding of 50 Gm. of mucin in water ce daily to eight M-W dogs.

We (507) subsequently made more thorough provisions for the control acidity in M-W dogs. We started by feeding large doses of aluminum droxide preparations to 40 of these animals without obtaining any neficial effect. Since gastric analyses showed that the treatment de-essed the acidity for only a short period following each dose of aluminum droxide, the experiments were extended to include 27 additional dogs hich were given the same preparation at hourly intervals from 8:00 A.M. 8:00 P.M. and another dose at midnight. In spite of the fact that there as no free acid in these dogs throughout the day, ulcers occurred in 0 per cent of the animals.

An arresting observation in this series of dogs was the early appearance anorexia, a symptom which ordinarily does not become manifest until e in M-W dogs. It occurred to us that this anorexia might be the result a phosphorus deficiency induced by the aluminum hydroxide. We were le to show (543) that aluminum hydroxide gel, when administered ng with an ordinary diet, interferes with the absorption of phosphates the dog; by means of experiments in which the small intestine was igated before and after the introduction of aluminum hydroxide, it s shown that the presence of the gel in the intestine in sufficient ncentration may extract phosphorus from the mucosa. In studies on mans, the administration of 240 cc. of 5 per cent aluminum hydroxide daily along with a light ulcer diet resulted in a 60 per cent decrease in urinary excretion of phosphorus. In view of these findings, we pre-red an aluminum phosphate gel and repeated the experiments on W dogs.

Twenty-three animals were given four doses of 100 cc. of the new paration daily in addition to a liberal diet: only three dogs developed ers. Even more striking than this unprecedentedly low incidence of er in M-W dogs on medical therapy was the healing effect of the minum phosphate. The treatment was discontinued in two animals t had not developed ulcer, as proved by exploratory laparotomy, ten nths after the M-W operation; both dogs lost weight and developed ical signs of jejunal ulcer after nine and 14 weeks respectively. After rapy was resumed, healing of the ulcers was demonstrated by lapa-omy in 16 weeks in the first dog and 11 weeks in the second. The eriment was repeated twice on the same dogs; after the third recur-ce, and resumption of aluminum phosphate therapy, the ulcer was d healed in four weeks in one dog, and five weeks in the other. In t other dogs in which therapy was discontinued until clinical signs of r appeared, resumption of the treatment was followed by healing of

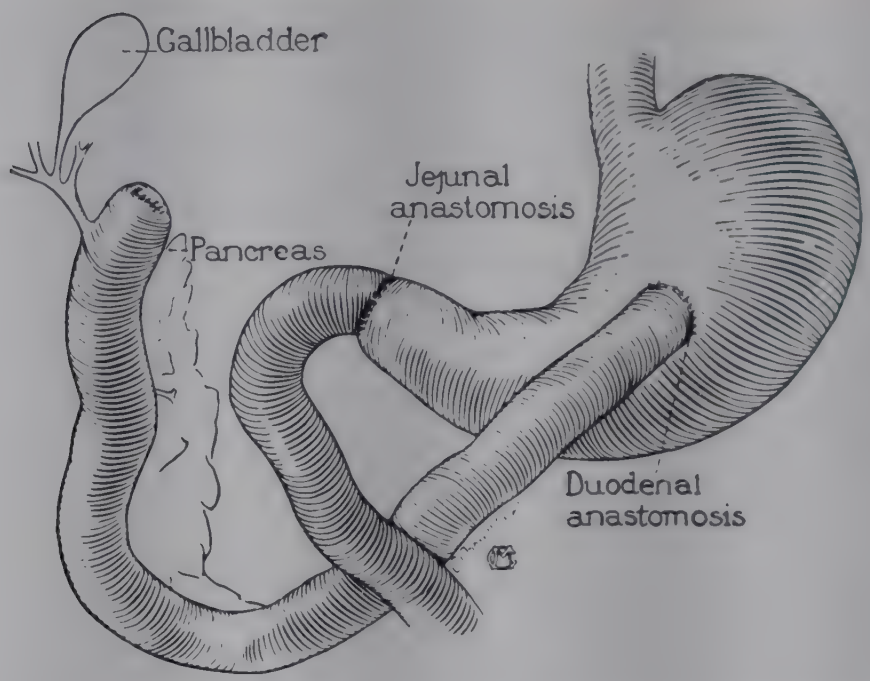


FIG. 77. Operative procedure, showing the duodenum draining the secretio of the gallbladder, liver and pancreas into the fundic portion of the stomac (Courtesy, McCann: *Arch. Surg.*, **19:** 600, 1929.)

the ulcers, as indicated by the presence of scars when the animals we sacrificed and autopsied.

The above results were obtained in spite of incomplete control of t acidity, free acid being found on numerous occasions several hours aft administration of a dose of the gel. It was also noted that dogs on alun num phosphate treatment developed a secondary anemia which w amenable to parenteral iron therapy.

Alteration in the Level of Duodenal Drainage: Drainage into the Stomac In 1921, Keppich (508) isolated a segment consisting of the pyloric antru and duodenum, and anastomosed it to the stomach near the cardia: t operation was completed with an end to side gastrojejunostomy. Bo dogs subjected to this procedure developed jejunal ulcer, whereas n lesions occurred in two dogs in which the operation was modified resection of the antrum. The author construed these results as an indi ment of the Eiselsberg exclusion operation for peptic ulcer.

McCann (509) drained the duodenal contents into the fundus of t stomach (Fig. 77) in 26 dogs; jejunal ulcer occurred in 80 per cent the animals. The postoperative gastric acidity values were stated by t author to be essentially the same as the preoperative values, so that t acid factor in the etiology of M-W ulcers was minimized by these expe ments. In dogs with the same operation, Maier and Grossman (510) not a decreased acidity and an increased ability to neutralize acid, and

urther decrease in acidity when the procedure was supplemented by artial gastrectomy (Fig. 78); only two cases of jejunal ulcer occurred in he series of 12 dogs.

When the duodenal contents were drained into the pyloric antrum Fig. 79), no ulcers occurred in the experiments reported by Weiss et al. 511), Graves (512), and Wilhelmj et al. (513); these studies comprised total of 31 dogs. Of 12 dogs in which we (503) carried out this pro-edure, only two developed jejunal ulcers. Of eight dogs in which the nastomosis of the duodenum to the stomach was resected and then nastomosed to the ileum, seven developed jejunal ulcer.

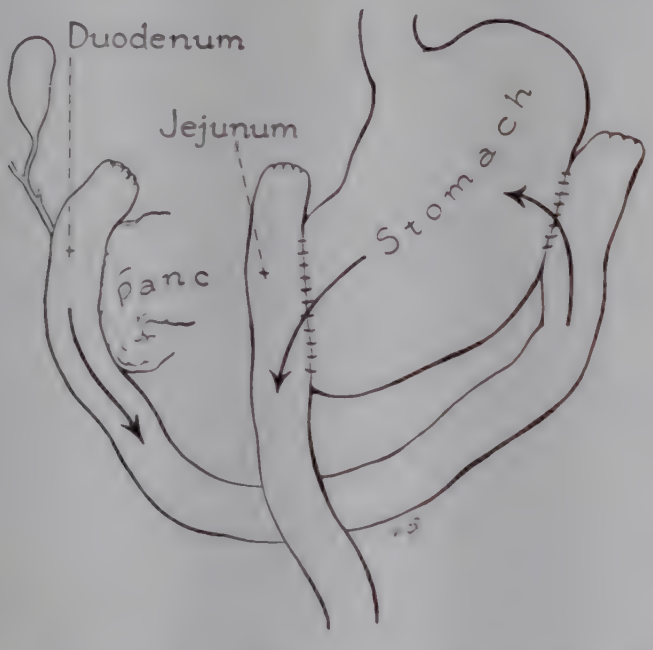


FIG. 78. Drainage of duodenal secretions into partially resected stomach. (Redrawn from Maier and Grossman: *Surgery*, **2:** 265, 1937.)

Wangensteen and co-workers (441, 442) sought to determine the cause r the large variation in the incidence of ulcer reported by various authors er the procedure of draining the duodenal contents into the stomach. noted above, McCann reported an 80 per cent incidence of ulcer lowing this operative procedure whereas all subsequent workers ported either that no ulcers developed or that the incidence was low. angensteen repeated the operation of McCann on eight animals; in lf of the dogs, the duodenal contents were drained into the fundus and the remaining half into the antrum of the stomach. Ulcer did not cur in any of these animals; therefore, it was concluded that the dis-pancy was not due to the site of drainage into the stomach. When,

however, Merendino and co-workers (443), working in Wangensteen' laboratory, performed the McCann operation on four dogs in whic the only variation in procedure was the use of a lower segment of jejunu for the gastrojejunal anastomosis, all died of spontaneous perforation of gastrojejunal ulcer. Wangensteen (442) attributed the lower incidence c ulcer when a high segment of jejunum was used to the richer secreti supply of the more oral intestine and assigned only secondary importanc to the inherent gradient in the susceptibility of the various levels of intes tine to peptic digestion. Further experiments (444) in Wangensteen'

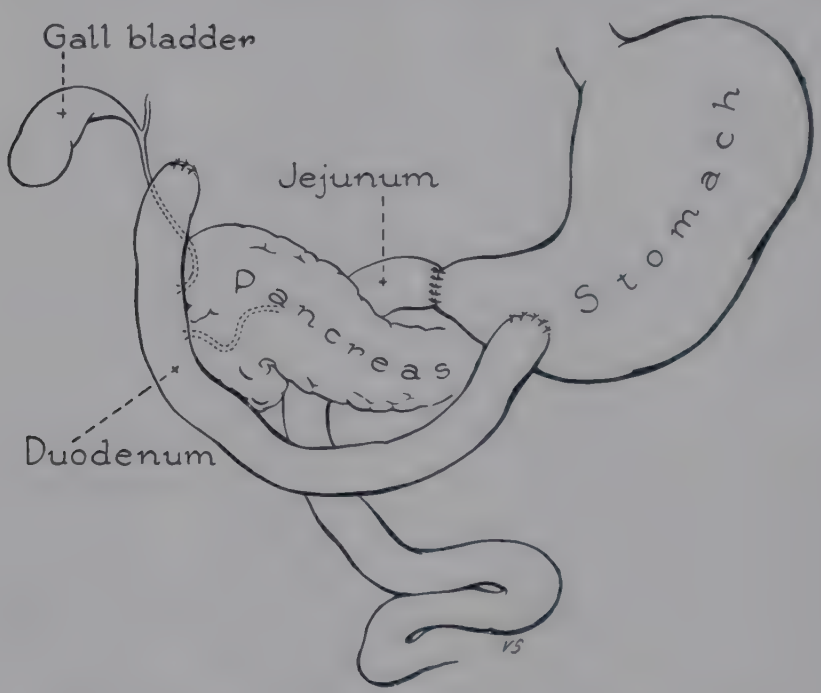
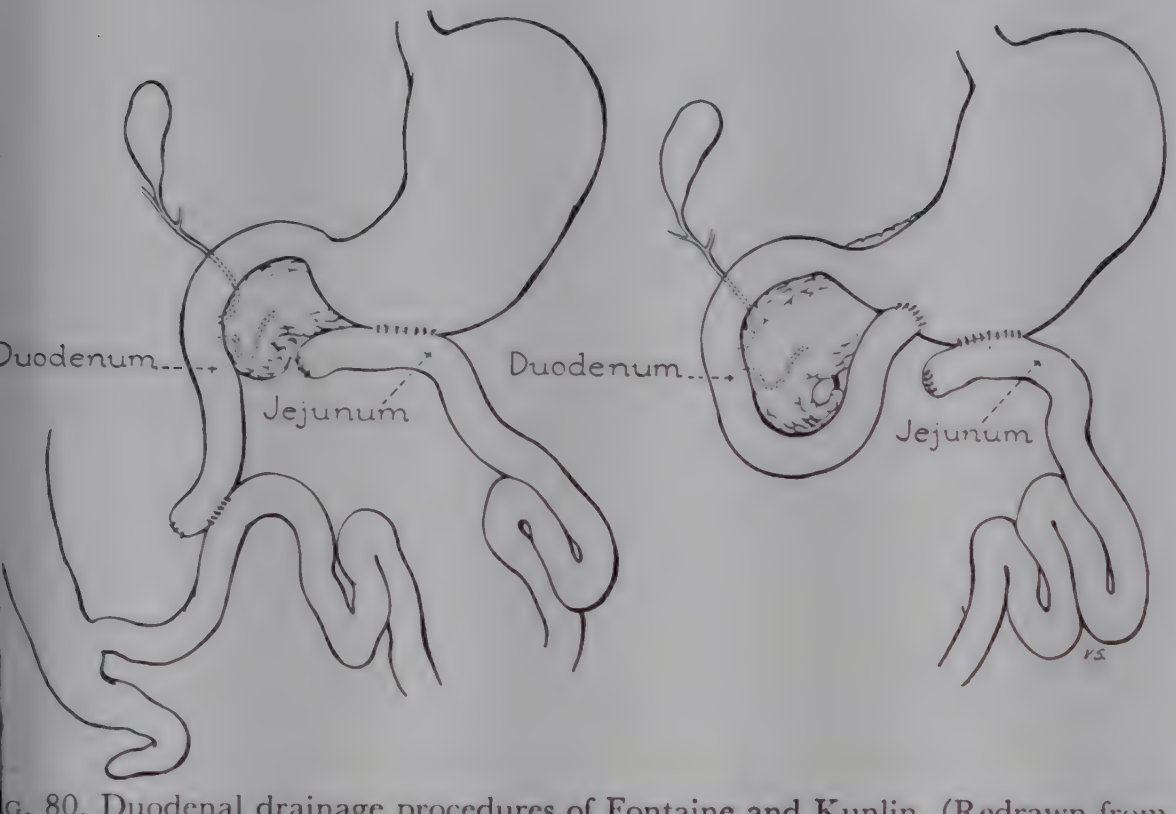


FIG. 79. Drainage of duodenal secretion into antrum. (Redrawn from Weiss: *Compt. rend. Soc. de biol.*, **109:** 916, 1932.)

laboratory tended to sustain the greater importance of the secretin facto and the factor of spatial separation of alkaline duodenal secretions fron acid gastric chyme. However, these conclusions must be considere tentative, pending the observation of a considerably greater number dogs than the authors presented in the report of their ingenious attack o this problem.

Regardless of the mechanism involved, it is of the greatest importanc to recognize that the distance from the pyloric sphincter of the piece intestine used for gastrointestinal anastomosis is an important factor i determining the outcome of all operations for experimental ulcer pr duction. It is probable that many apparent discrepancies in the literatu could be resolved if the exact details were known about the level gastrointestinal anastomosis in each case.



G. 80. Duodenal drainage procedures of Fontaine and Kunlin. (Redrawn from *Compt. rend. Soc. de biol.*, **110:** 294, 1932.)

Owings and Smith (482) anastomosed the isolated duodenum to the omach in seven M-W dogs after ulcers had already formed; partial or mplete healing ensued in six cases.

Fontaine and Kunlin (514) attempted to repudiate the loss of duonal secretions as a cause of ulcer in M-W dogs by means of the operans shown in Fig. 80, in which the pylorus was left intact. The operation ustrated by the first sketch was performed in two dogs, one of which had be excluded from the series because the gastrojejunostomy became structed by concretions; the remaining dog developed a jejunal ulcer. hen the duodenum was anastomosed to the stomach in two other dogs, th developed ulcer. These findings were not confirmed by Santoro 5), who concluded that the regurgitation of duodenal secretions yed an important role in the prevention of jejunal ulcer. It may be ntioned that these experiments are similar to those reported in 1898 Chlumskÿ (516), whose dogs died too early to permit any conclusions g. 81).

Drainage into the Jejunum. Matthews and Dragstedt (79) drained the odenal contents into the jejunum just distal to the gastrojejunostomy l placed a valve in the jejunum proximal to the site of drainage to vent the regurgitation of biliary and pancreatic secretions (Fig. 82). hough the acidity of the gastric contents was little affected by this cedure, six of the 10 dogs developed ulcers. In view of the frequent

demonstrations in the older literature (for example, Exalto: 456) tha the gastrojejunostomy en-Y (Roux) was followed by a high incidence o jejunal ulcer, one might question the significance of Matthews an Dragstedt's findings; but more recent experiments would indicate tha ulcer rarely occurs when the duodenum is drained or anastomosed short distance below the gastrojejunal anastomosis. Thus, Gallagher an Palmer (481) observed no ulcers when the drainage was placed 9.5, 12 and 15 cm. respectively from the gastrojejunostomy. Similar results wer reported by Wilhelmj and associates (513). However, Fiessinger an Palmer (517) produced ulcers in two dogs by the Y-anastomosis.

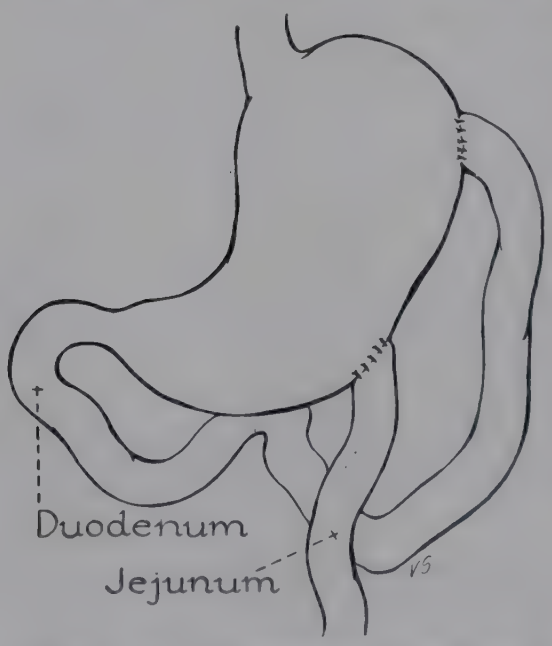


FIG. 81. Intragastric duodenal drainage according to Chlumsky. (Redrawn from *Beitr. z. klin. Chir.*, **20:** 231, 1898.)

Mann (518) and Morton (519 made the important observation tha if the gastrojejunostomy in M-W dogs is taken down after an ulcer ha developed and a new anastomosi made more distally, the original ulce heals while a new ulcer forms in th jejunum at the site of the new gastro jejunal stoma.

Implantation of the isolated duo denum at various distances below th gastrojejunostomy brings in the fac tor of nutrition, and experiments o this type have already been reviewe under that heading.

Determination of the Gastric Acidi in Mann-Williamson Dogs. In a revie of the literature on the surgica methods of producing peptic ulce Ameline and Jonckheere (520) stated that "the chemical theory, attribu ing the genesis of ulcer to the hyperacidity provoked by the diversion o the alkaline duodenal liquids, can no longer be supported in view of th demonstration of the constancy of the normal acidity of the stomach i experimental ulcer."

This conclusion was based on the data presented by McCann (50 and by the repeated statements (unsupported by figures) of the Frenc investigators that there was no difference in the gastric acidity followi the M-W operation in dogs. Fig. 83, taken from McCann, shows graphic form the preoperative and postoperative acidities in a typic M-W dog; the author interprets the curves as indicating that the oper tion produces no difference in the acidity, and that an intragast neutralizing mechanism is present which is able to compensate for th

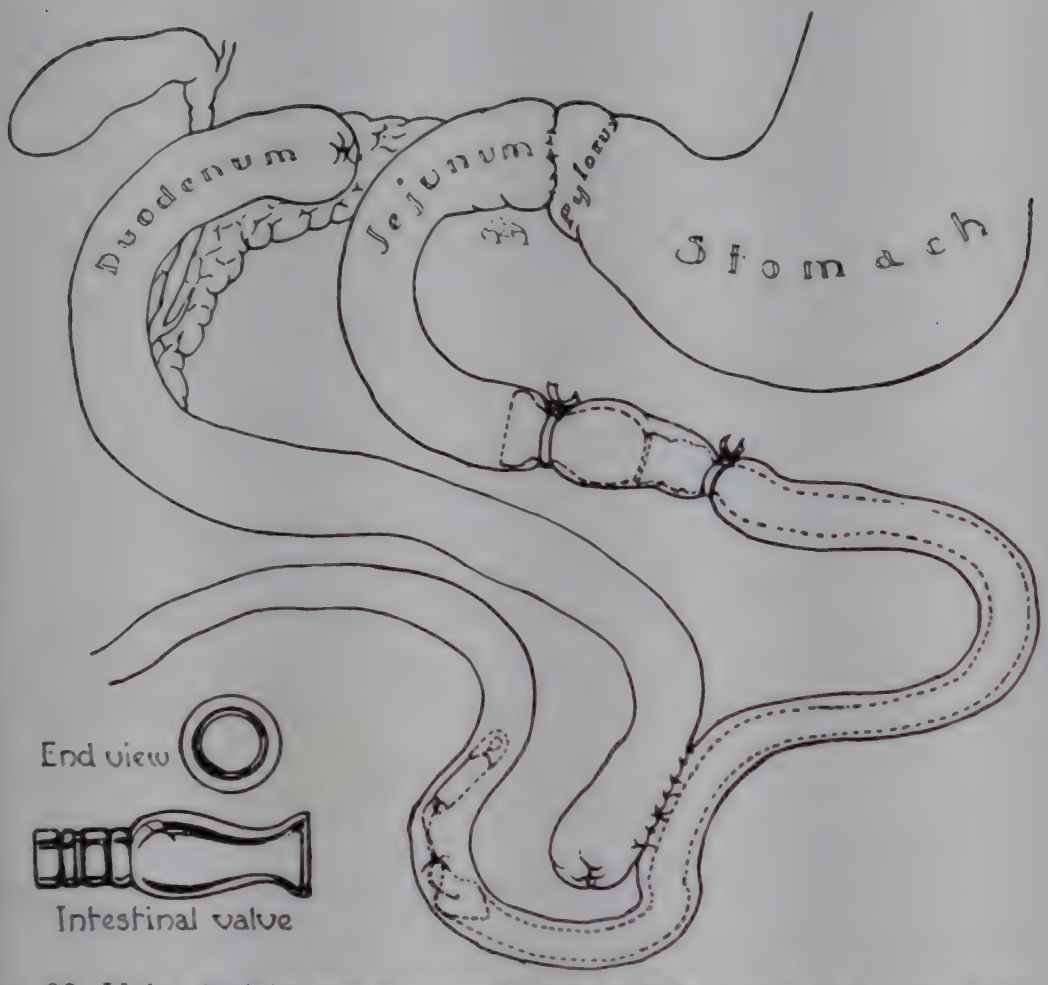


FIG. 82. Valve in jejunum proximal to site of drainage of duodenal contents preventing regurgitation of alkaline juices to the region of the gastrojejunostomy. (Courtesy, Matthews and Dragstedt: *Surg., Gynec. & Obst.*, **55:** 265, 1932.)

sence of the neutralizing action of the duodenal secretions. It is odd at he does not attribute some significance to the more prolonged elevan of the acidity after operation in response to the test-meal.

We (473, 507, 521) have demonstrated repeatedly that an increased tput of acid frequently follows the Mann-Williamson operation (Fig.); this is doubtless attributable in part to the diversion of the duodenal ntents, but we have obtained evidence which we interpret as indicating t a part of the increase is due to the formation of excessive amounts of tamine in the irritated jejunal mucosa. In three Pavlov-pouch Mann-lliamson dogs, we (521) found that atropine did not abolish the gastric retory response to a meat meal, indicating that after the M-W operation gastric secretory mechanism reacts as though a portion of the secretory nulus were histamine.

In a careful analysis of the gastric secretion in five dogs before and r the M-W operation, Wilhelmj and Finegan (522) demonstrated that drop in acidity which occurred within an hour after administration Liebig's extract test-meal in the normal dog did not take place after

drainage of the duodenal secretions. The authors attributed these findings to the fact that the regurgitation of nonacid secretions from the duodenum is prevented by the operation.

Wu (523) studied the reaction of the jejunum before and after the M-W operation by obtaining samples of the jejunal content through a fistula at the site where the ulcers form. The results showed quite definitely that after operation the jejunal mucosa was exposed not only to a more acid medium but to one in which the fluctuations of acidity were greater than normal.

Slive et al. (477) could establish no clear-cut relationship between postoperative acidity levels and the incidence of jejunal ulcer; however, it may be noted from their data that a more prolonged average secretion of acid was present preoperatively in the group of dogs which developed ulcers after the modified M-W procedure. If similarly quantitative work could be carried out in humans, it might prove practicable to determine which duodenal ulcer patients are likely to develop jejunal ulcer after gastric resection.

Comment. The evidence supporting the acid theory of the origin of postoperative jejunal ulcer may be summed up as follows:

1. Chronic perforating ulcer develops in the intestine exposed to the action of pure gastric juice even though the general health of the animal is maintained.

2. The incidence of jejunal ulcer following duodenal drainage is markedly reduced by a simultaneous partial gastrectomy or fundusectomy.

3. The development of ulcer in M-W dogs is partially or completely

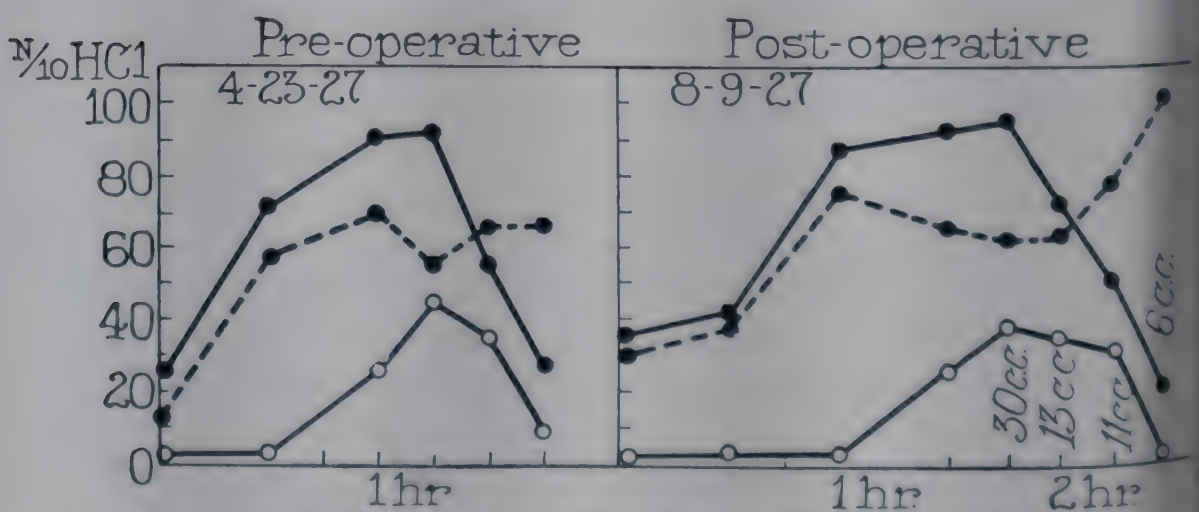
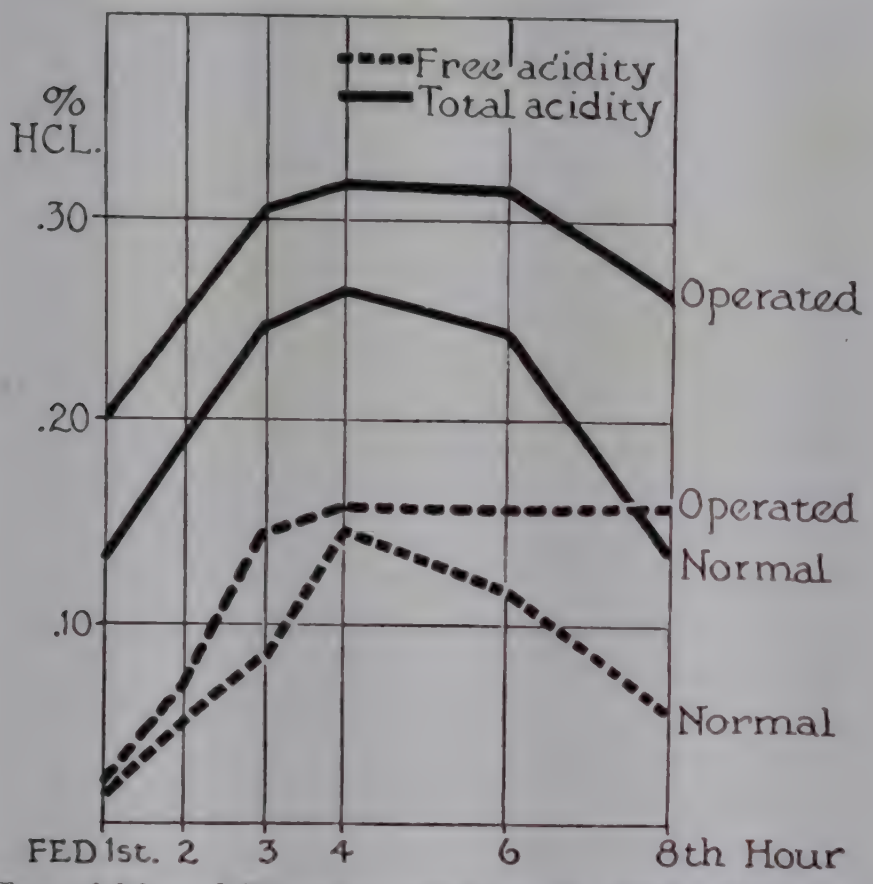


FIG. 83. Character of curves in response to a test meal before and after the surgical drainage of the duodenal alkalis from the pylorus into the distal part of the ileum. The solid line with the hollow circles indicates the free hydrochloric acid; the solid line with the solid circles, the total acid; and the broken line with the solid circles, the combined chlorine. (Courtesy, McCann: *Arch. Surg.*, **19**: 600, 1929.)



G. 84. Effect of Mann-Williamson operation on gastric secretion. (Courtesy, Fauley et al.: *Am. J. Digest. Dis. & Nutrition*, 5: 792, 1939.)

evented by either surgical or medical measures which reduce or elimi-ite the secretion of acid.

4. In most M-W dogs, there is an abnormally prolonged secretion of stric juice in response to a test-meal.

5. If the site of the gastrojejunal stoma is moved distally after a jejunal cer has formed, the ulcer heals while a new one forms opposite the new astomosis.

6. Gastrectomized dogs with esophagojejunal anastomosis do not velop ulcer, whereas dogs with gastrojejunostomy not infrequently velop ulcer.

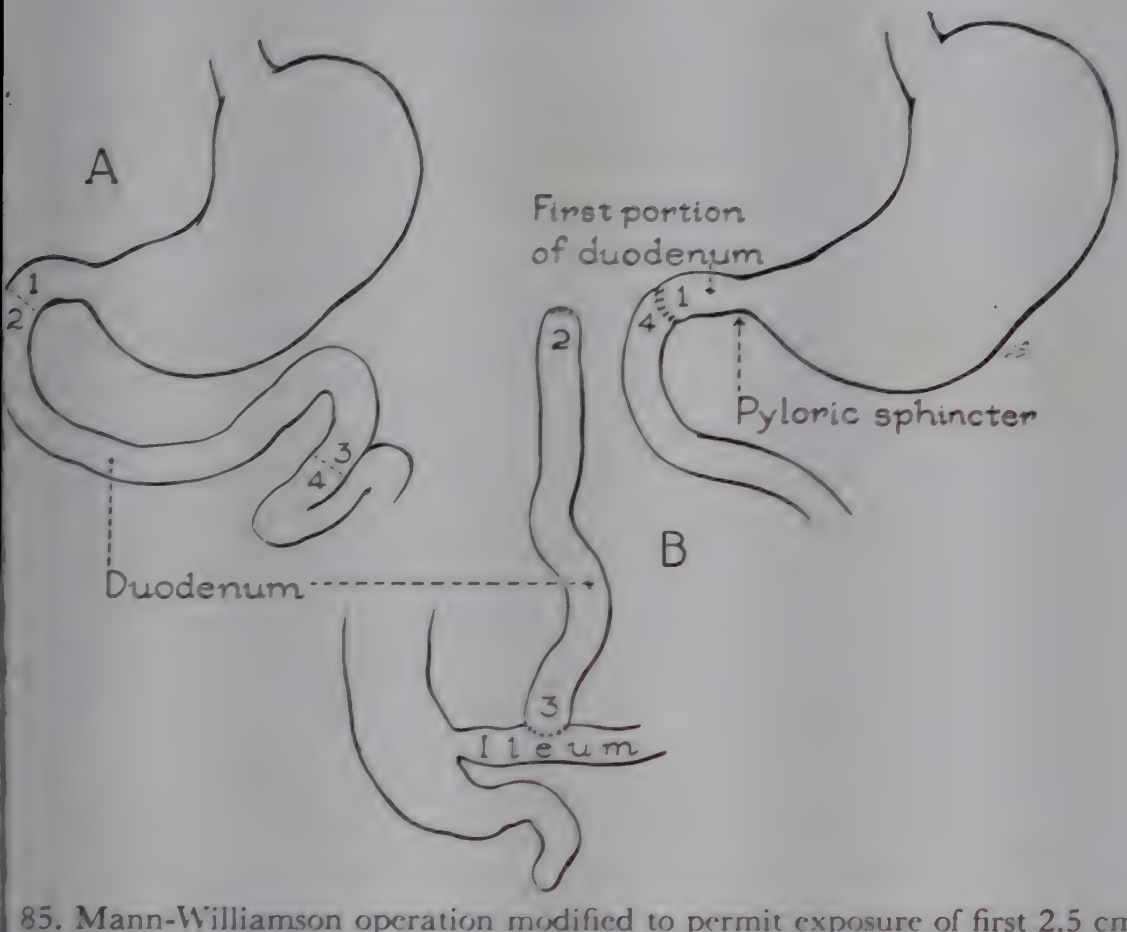
The hypersecretion of gastric juice in M-W dogs takes on added nificance when it is remembered that the exposure of the jejunal ucosa to the normal acidity of the stomach in a patch transplant does t result in ulceration (see Chapter 5). It is reasonable to assume that the hanced interdigestive secretion of gastric juice noted in M-W dogs is rticularly important because it permits the action of gastric juice buffered by food.

Some workers in the field of experimental ulcers; e.g., Schiffrin (524), gelson (526) and LeVeen (438), have taken issue with the tendency to ce full responsibility for the primary etiology of experimental ulcer on the

acid factor without a consideration of pepsin. This objection is, to a cert
extent, justified because it has never been demonstrated that acid al
in the absence of pepsin can produce ulceration. For instance, Schiff
(524) demonstrated that perfusion of the stomach with acid alone n
cause ulceration because pepsin appears in the perfusate, whereas p
fusion of the jejunum with acid alone causes only superficial damage unl
unphysiologic pressures are used. On the other hand, the thesis f
enunciated by Matthes (525) (see Chapter 4) appears still to be tena
namely, that acid first produces devitalization and that peptic activ
then removes the devitalized tissue so that the acid may act anew up
deeper tissues. Therefore, while it is undeniable that pepsin is necessa
together with acid in order to produce actual ulceration, certain co
siderations indicate that acid does, in fact, hold a predominant positi
These considerations are: (a) pepsin is always present in acid gastric ju
(the converse is not true); (b) no elevation in the concentration of pep
occurs in M-W dogs or in dogs receiving histamine in beeswax (52
(c) acid alone can cause devitalization and all the evidence indicates th
pepsin can act only on devitalized tissue. The possibility remains th
pepsin enhances the devitalizing action of hydrochloric acid in some w
other than the exposure of fresh surfaces (e.g. by releasing histamin
this awaits proof. In the final analysis, the question is somewhat sophist
involving as it does an attempt to assign predominance to one of tw
mutually interdependent factors.

The Factor of Mucosal Susceptibility. According to Langenskio
(465), when the duodenum was deprived of its alkaline secretions
ligation of the bile and pancreatic ducts, it exhibited no greater resistan
to perfusion with juice from a Pavlov pouch than did a loop of jejunu
Although in his experiments there was evidence that the jejunum w
more readily attacked, the author attributed this to technical errors.

Kehrer (464) anastomosed the gall bladder and pancreatic ducts
the appendix or terminal ileum; duodenal ulceration occurred in on
one of the nine dogs operated upon. Of the other investigators who studi
the effects of similar operations, the incidence of duodenal ulcer w
reported as 10 out of 31 by Mann and Williamson (467), two out of fo
by Grey (528), and none out of four by Paolucci (529). This incidence
obviously much lower than that which occurs in the jejunum deprived
bile and pancreatic juice. Conversely, when the jejunum was substitute
for the duodenum by the operation of duodenectomy, gastrojejunosto
and implantation of the ducts into the jejunum, Mann and Kawam
(530) obtained jejunal ulcer in two of 11 dogs observed from 10 to
months; the same procedure supplemented by subtotal gastrectomy



85. Mann-Williamson operation modified to permit exposure of first 2.5 cm. of duodenum to same concentration of acid as acts on jejunum.

result in a single case of ulcer in seven dogs surviving for a similar od of time (531).

McCann (509) and we (532) are agreed that if the M-W operation is lified so that the first part of the duodenum is anastomosed to the num, and the rest of the duodenum (containing the ducts) is drained the ileum (Fig. 85), ulcers occur only in the jejunum and not in the denum, although both are subjected to identical conditions.

Working with pigs, Florey and his associates (499) tested the com- tive resistance of the duodenum and ileum by anastomosing segments testine to a Pavlov pouch, according to the method of Matthews 332). No ulceration occurred in any of the seven pigs in which the gastric juice emptied into the duodenum, whereas in all of the three with pouches anastomosed to the ileum, perforated ulcers of the tinal loop were found at autopsy. The authors ascribed the protection e duodenum to the presence of mucoid secretions from Brunner's ds.

Comment. The foregoing experiments, as well as the evidence presented hapters 4 and 9, indicate that the upper duodenum is more resistant

to ulceration than the rest of the small intestine. This increased resistance of the upper duodenum can logically be attributed to the protective action of the secretion of the Brunner's glands present in this area. There also appears to be a gradient in the resistance of the small intestine below the level of Brunner's glands and this is obviously of some importance in human surgery.

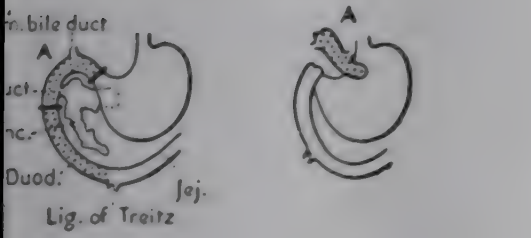
This question has received the attention of Wangensteen and co-workers (436, 442). In their investigations, a three-quarter resection of the stomach was performed and an anastomosis of the end of the stomach to the side of the intestine accomplished. In a series of 11 dogs in which the anastomosis was done 12 to 15 cm. from the duodenal stump and the animals, after recovery from the operation, were given histamine in bees-wax (see p. 213), no ulcers appeared. When the identical operation, with the exception of placing the anastomosis 27 to 78 cm. from the blind duodenal end, was performed in seven dogs and again histamine in bees-wax was administered, each of the dogs in this group developed jejunal ulcers. A third group of four dogs was subjected to gastric resection and the anastomosis placed 78 to 144 cm. from the inverted duodenal end. No histamine was given to these animals. Two of the four dogs developed spontaneous perforation of jejunal ulcers. These experiments constitute strong evidence of the increasing susceptibility of the intestinal mucosa as the distance from the pylorus becomes greater.

A further study of the factors which are involved in the increased susceptibility to stomal ulcer when a long afferent loop is employed was carried out by Wangensteen's group (444). The experiments attempted to determine which of three theoretically possible factors is most important in the genesis of stomal ulcer. The three items which were considered are (1) the secretin factor (i.e. lower concentration of secretin in the more aboral gut), (2) the factor of spatial separation of alkaline and acid digestive secretions, (3) the mucosal sensitivity factor (increased susceptibility to injury by acid-pepsin of lower segments of bowel). Six different operative procedures were employed (Fig. 86). The results were interpreted by the authors as being inconclusive concerning the relative importance of the secretin and "distance" factors, but indicating that these two factors are more important than the "sensitivity" factor. The authors failed, however, to take into consideration the nutritional factor, which was certainly considerably affected in some of their operative procedures.

Mann has described experiments in which loops of duodenum, jejunum, and ileum were transplanted to the point of emergence of the gastric content in M-W dogs. The duodenal mucosa was found to be most resistant to the formation of ulcer, the mucosa of the ileum least resistant, and that of the jejunum intermediate between the two. Simi-

Experiment 1

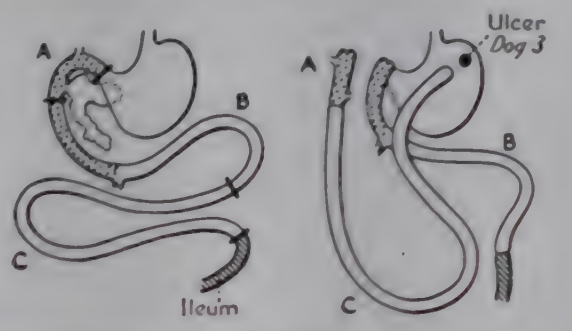
Short Afferent Loop and Efferent Gastroduodenostomy



Length of Seg. A	Survival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
8 cm.	72 da.	Sacrif.	No	Good
9 cm	88 da.	Sacrif.	No	Good

Experiment 2

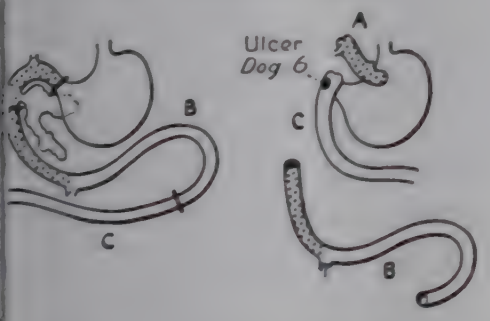
Long Afferent Loop (segment of lower jejunum interposed between afferent duodenum and stomach) and **Efferent Gastroduodenostomy**



Dog No.	Length of Seg. A + Seg C	Survival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
3	85 cm.	150 da.	Perit.	Yes	Good
4	85 cm.	185 da.	Sacrif.	No	Good

Experiment 3

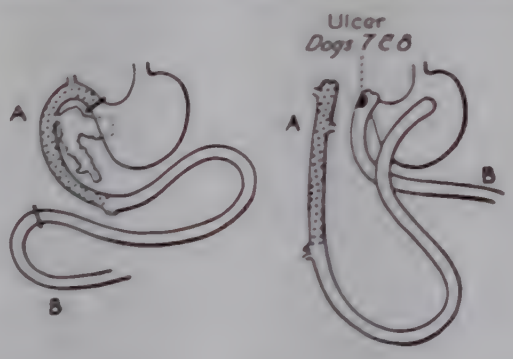
Afferent Loop, partial duodenojejunectomy, and **Efferent Gastrojejunostomy**



Length of Seg. A	Exc. seg. B	Survival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
10 cm.	75 cm.	81 da.	Sacrif.	No	Poor
8 cm.	75 cm.	77 da.	Obs. aff. L.	Yes	Poor

Experiment 4

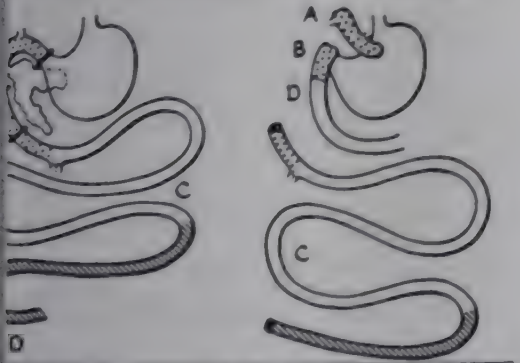
Long Afferent Loop and **Gastrojejunostomy**



Dog No.	Length of Seg. A	Survival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
7	75 cm.	150 da.	Perf. ulc.	Yes	Poor
8	90 cm.	55 da.	Perf. ulc.	Yes	Poor

Experiment 5

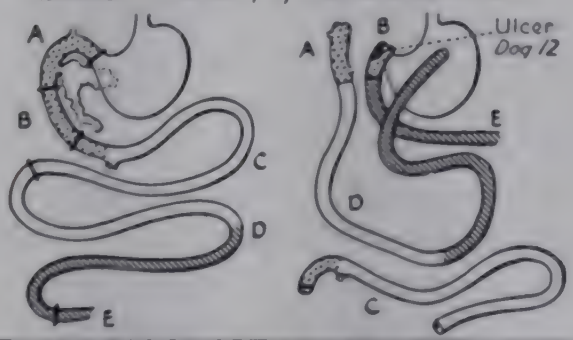
Afferent Loop, partial duodenojejunectomy, **Efferent Gastroduodenostomy**, and restoration of continuity by **Duodenoileostomy**



Length of Seg. A	Seg. B	Exc. seg. C	Survival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
2 cm.	7.5 cm	135 cm.	85 da.	Sacrif.	No	Satis., ?
7 cm.	4 cm.	135 cm.	53 da.	Sacrif.	No	Satis., ?

Experiment 6

Long Afferent Loop (interposition of lower jejunoileal segment between afferent duodenum and stomach), partial duodenojejunectomy, **Efferent Gastroduodenostomy**, and restoration of continuity by **Duodenoileostomy**



Dog No.	Length of Seg. A + D	Seg. B	Exc. seg. C	Survival period	Cause of death	Ulcer at autopsy	Theoretic secretin produc.
11	90 cm.	12 cm.	60 cm.	81 da.	Sacrif.	No	Good
12	90 cm.	3 cm.	60 cm.	75 da.	Perf. ulc.	Yes	Satis., ?

IG. 86. A study of the factors concerned in the relationship between length of nt loop and stomal ulcer. (Courtesy, *Proc. Soc. Exper. Biol. & Med.*, **58**: 1945.)

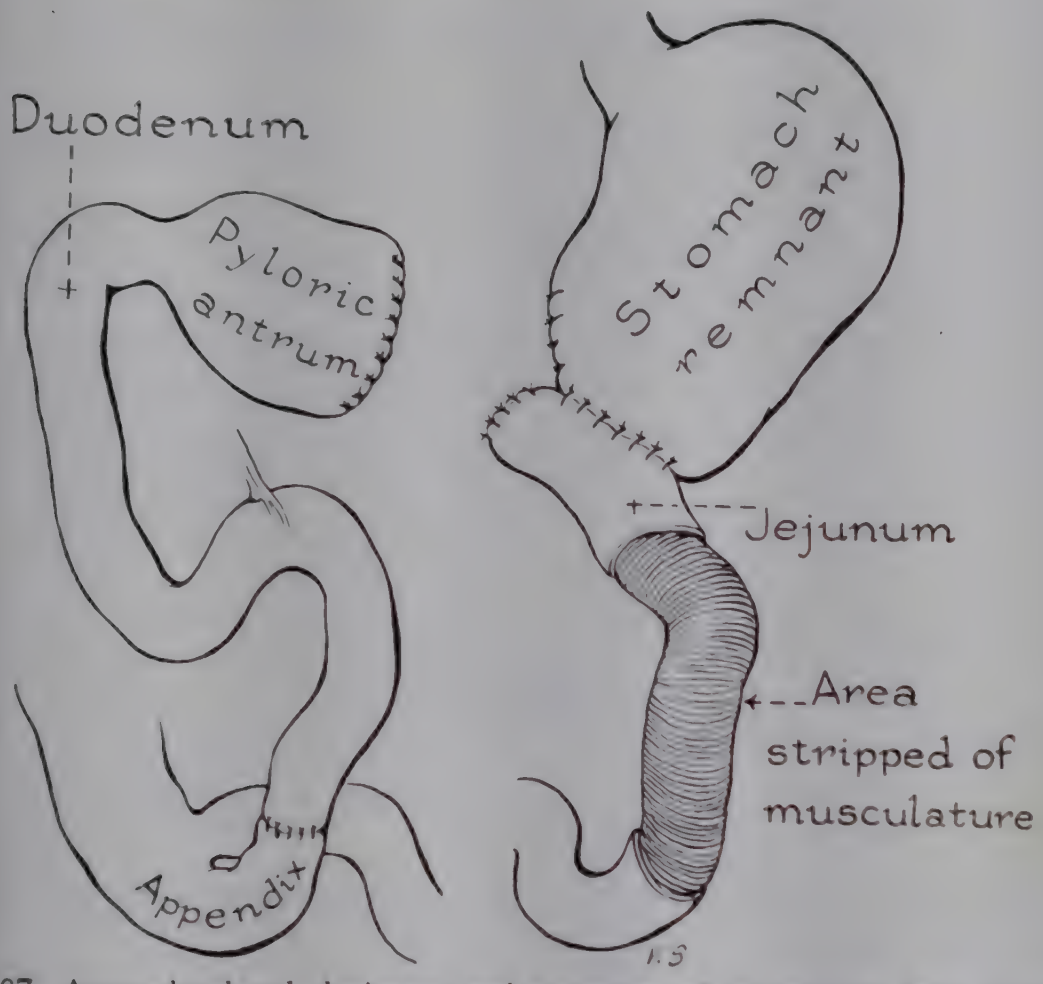
results were obtained by employing a fundic pouch drained by a loop o intestine from the three main regions of the intestinal tract.

Mechanical Factors. It was suggested by Mann (475) that th destruction of the pyloro-duodenal mechanism might be a factor in th etiology of ulcer in M-W dogs. According to this view, the propulsion of nozzle-like stream of chyme through a narrow gastrojejunal stoma woul explain the location and singleness of the ulcer; the occurrence of contac ulcers would then be due to a splitting of the force of the stream. Mann stated that animals in which the propulsive action of the stomach wa greatly decreased by experimental creation of an hour glass stomach proved most resistant to the development of ulcer. Similarly, Steinberg and Proffitt (451) attributed the low incidence of ulcer in M-W dogs with gastric resection to the removal of the muscular drive of the pyloric antrum. These authors recommended a large anastomotic opening be tween the fundus and jejunum as the best method of preventing jejuna ulcer; but, as has already been mentioned, one might just as easily attribute their good results to reduction in the gastric secretion. The experiments of Winkelbauer and Hogenauer (533) on this subject were terminated too soon to be of any significance, but it has been pointed out that the evidence regarding the prevention of ulcer in M-W dogs by antrectomy is not conclusive. Also, it should be recalled that Beaver and Mann (504) and others (see p. 337) were unable to prevent ulcers in M-W dogs by vagotomy, which presumably reduced the motor activity of the stomach to a considerable extent.

Leriche et al. (534) contend that the site and number of ulcers following duodenal drainage depend on the type of gastrojejunostomy. An end to end anastomosis results in a single jejunal ulcer with occasional pyloric ulcer; a side to side anastomosis results in multiple jejunal ulcers with occasional pyloric ulcer; and, when the stomach is sectioned proximal to the pyloric antrum, the latter closed and drained along with the duodenum and the operation completed by a side to side gastrojejunostomy, the result is always multiple jejunal ulcer. According to Mann, if the intestine which is anastomosed to the pylorus is made to run in the same direction as the pylorus for a short distance and then is bent acutely, the ulcer will develop just proximal to the bend. In such experiments, the ulcer may be made to develop 15 cm. distal to the usual site of formation.

Weiss and Hubster (535) attempted to interfere with the motor coordination of the upper digestive tract by dividing and immediately suturing the antrum, the pylorus, and the duodenum below the papilla; no ulcers were produced.

Deloyers (192) considered mechanical factors of little importance, since he found that ulcers appeared with equal frequency when the



G. 87. Antro-duodenal drainage and stripping of muscularis from jejunum. (Redrawn from Winkelbauer: *Arch. f. klin. Chir.*, **143**: 649, 1926.)

strojejunostomy was made in the more active pylorus or in the less tive fundus. In this regard, it was shown in Chapter 5 that, when, in a -W dog, a pedicled patch of jejunum is placed in the stomach, an ulcer curs in the jejunum opposite the gastrojejunostomy orifice and not in e patch. Here the factors of acid-pepsin and nutrition are the same, and would seem that the only other factor that might be different is the echanical factor.

Operative Trauma. Mann (475) considered it quite certain that erative trauma is not responsible for ulcers in M-W dogs, and this has en confirmed repeatedly. It was shown by Denk (466), Gallagher (536), d Gallagher and Palmer (481) that the application of clamps at the time operation did not result in chronic ulcers. This is ordinarily true; never-eless, clamps may produce acute ulcers in the duodenum and jejunum, d such a lesion may occasionally go on to chronicity. Thus, Gallagher d Palmer (481) observed that in a few instances the ulcers at the site the clamp lesions persisted although, in addition, the typical M-W ulcer peared at its usual site opposite the gastroenteric stoma. Of similar port were our experiments (41), in which duodenal ulcers occurred in

five out of 40 dogs in which gastroduodenostomy was performed clamps.

The use of silk as suture material has occasionally been said to dispose to ulceration at the point where the sutures pass through jejunum, but this has not been a significant factor in our experience as well as that of Scott (537) and others. A large silk knot may obvi be a hazard, especially if the mucosa is evaginated so that it prot into the lumen of the bowel (41), but this is a matter of surgical techn

The Factor of Jejunal Spasm. In an attempt to prevent spas the jejunum in the region where it receives the gastric contents, W

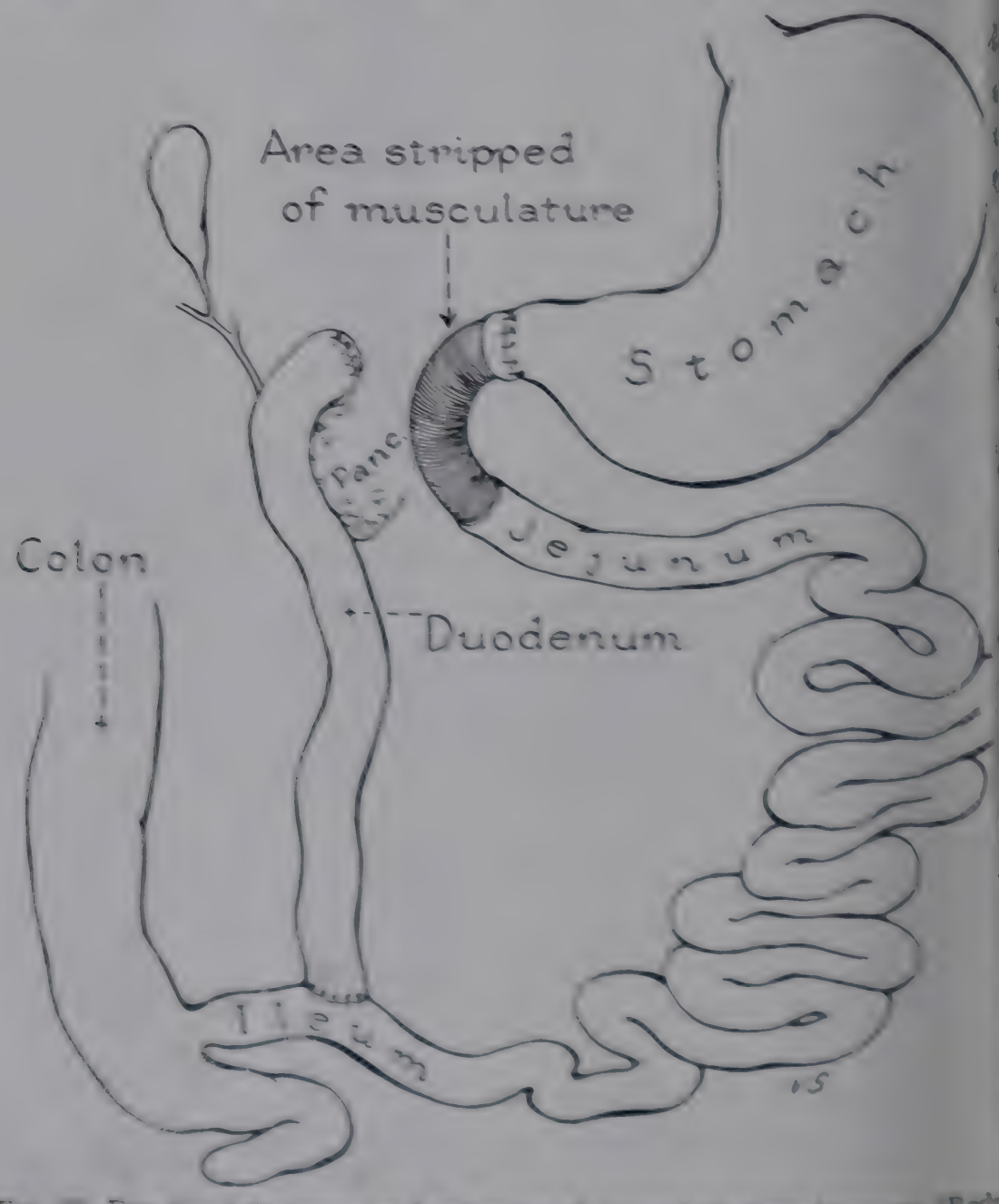
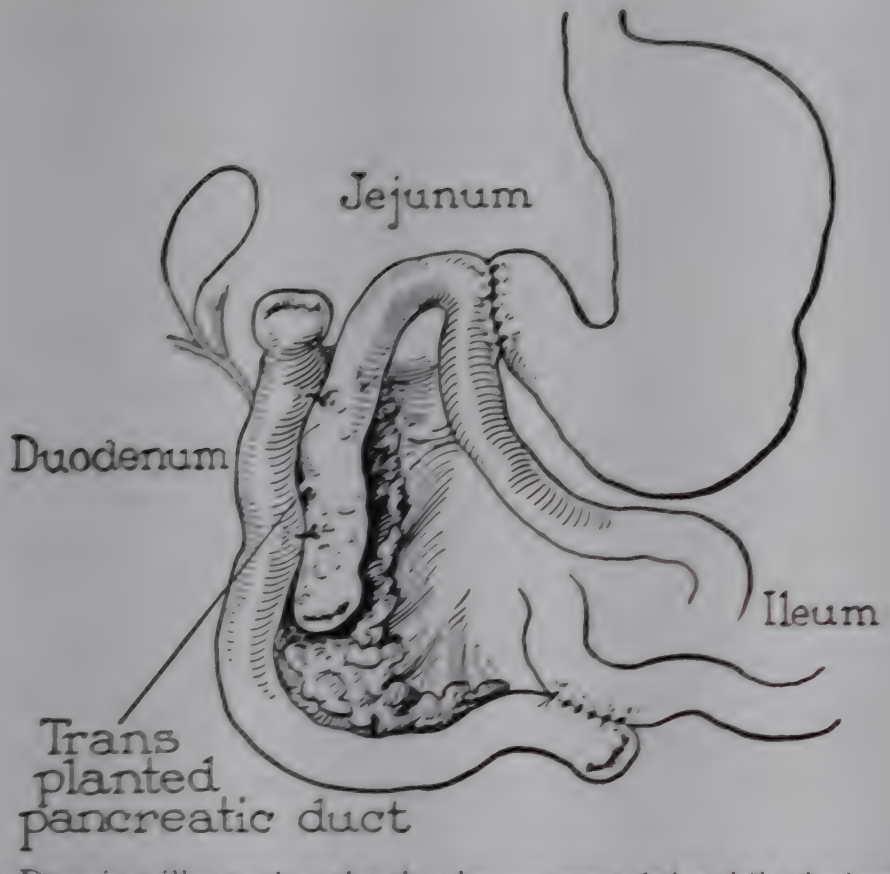


Fig. 58. Duodenal drainage and stripping of muscularis from jejunum. [Redr from Sonnenberg and Starr, *Arch. Surg.*, **29**: 856, (1934).]



. 89. Drawing illustrating the duodenum containing bile drained into the and substitution for it of the jejunum containing the transplanted pancreatic (Courtesy, Graves: *Arch. Surg.*, **30**: 833, 1935.)

(492) stripped the muscularis of the jejunum for a distance of 15 to . distal to the gastrojejunostomy in dogs with duodenal drainage 87). The one animal which lived long enough to be of any signifi- did not develop ulcer. The experiment was repeated by Steinberg is co-workers (538–540), who reported that in M-W dogs with the l musculature removed for a distance of 10 cm. distal to the anasto- (Fig. 88), no ulcers occurred in the area where the jejunum was ed of its muscularis; in every case, the lesions occurred either nt to the anastomosis, proximal to the point where the stripping of unum was begun, or just at the site where the muscle layer began mal course. We (532) repeated these experiments in 15 dogs, and ed ulcers in the stripped portion of the jejunum in 13 cases.

OTECTIVE ACTION OF THE DUODENAL SECRETIONS. The French in- tors have attributed postoperative jejunal ulcer to the absence of otective action of bile and pancreatic juice—not in the sense that ecretions neutralize the gastric acidity, but by virtue of the fact ey line or carpet (tapissement) the intestinal mucosa so that it be reached by the gastric juice. Fiessinger and Palmer (517) state, ample, that an "ulcere de sortie" will form wherever the gastric

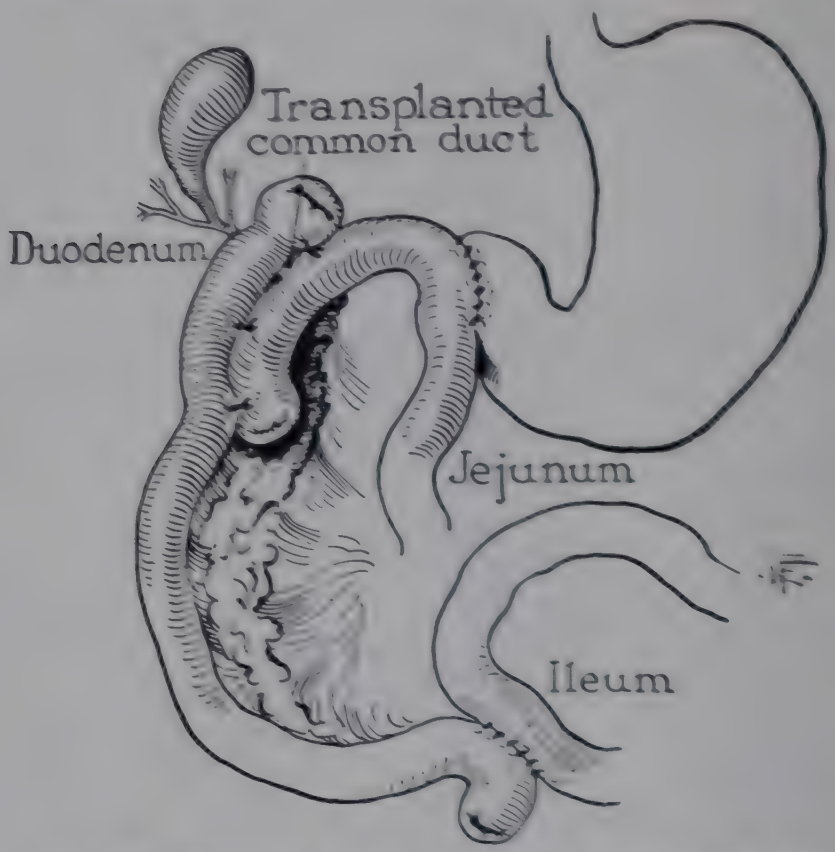


FIG. 90. Drawing illustrating the duodenum containing pancreatic juice drained into the ileum and substitution for it of the jejunum containing the transplanted common duct. (Courtesy, Graves: *Arch. Surg.*, **30**: 833, 1935.)

juice strikes the intestinal mucosa when the bile and pancreatic juice have not previously or simultaneously arrived at the same site. The concept is based in part on the assumption that the neutralizing action of bile and pancreatic juice is negligible. In this regard, the recent work of Barry and Florey (489) and of Berman and Baxter (541) attribute considerable importance to the secretion of Brunner's glands of the duodenum in protecting the upper intestine from ulcerations.

The relative protective value of the duodenal secretions has been the subject of some investigation. Bauer and Aron (542) concluded, from observations on one dog, that the secretions of the duodenal glands played a predominant role over bile and pancreatic juice in protecting the duodenum from ulceration. Graves (512) undertook to determine whether bile or pancreatic juice was more effective in preventing postoperative jejunal ulcer. In his experiments, the main pancreatic duct was transplanted to the jejunum near the site of the gastrojejunostomy, and the duodenum was drained into the ileum (Fig. 89); five dogs with this operation all developed ulcers. Identical results were obtained when bile alone was supplied to the upper jejunum (Fig. 90). DeBakey (455) performed a gastrojejunostomy with interruption of the pylorus in 20 dogs; jejunal ulcer developed in 50 per cent. The same operation supplemented by

stomosis of the pancreatic duct to the ileum was followed by ulcers in per cent of 10 dogs; when the common duct, instead of the pancreatic t, was transplanted to the ileum, the incidence of ulcer was 90 per cent 0 dogs. Finally, when both the bile and pancreatic ducts were anastosed to the ileum in 10 dogs with previous gastrojejunostomy, ulcer urred in all of the animals. The author therefore concluded that bile the most important factor in preventing jejunal ulcer, while pantic juice was intermediate and succus entericus was of least importance. While the experiments just outlined deal with the role of the respective denal secretions in postoperative jejunal ulcer, the relation of bile pancreatic juice to peptic ulcer in general has been the subject of rate investigations, which are described in Chapter 9.

Summary

There is no good evidence showing that ulcers are caused by the onged administration of irritating condiments. Salicylates given y may cause gastric ulcer, but it is not certain that these drugs act y by gastric irritation. They may, however, serve as a predisposing r. That external trauma such as blows to the abdomen and tight g cause chronic ulcer has not been proven. The exposure of the ic mucosa to an appropriate dose of x-rays produces a chronic ulcer h is apparently due to the excessive fibrosis which develops in the and margins of such an ulcer.

t has been demonstrated that streptococci can be isolated from most s of the stomach and duodenum and that their intravenous injection cause acute lesions of the mucosa. The mechanism of "elective ty" or "selective localization," when it has occurred, is uncertain. uld appear from the evidence that to obtain a "chronic" ulcer, other rs must be associated with the infection.

igh-grade gastric retention delays the healing of an experimentally ced acute ulcer of the gastric mucosa, but it does not cause an acute to develop, except in complete pyloric obstruction in the rat. This rms with observations in man in which patients with duodenal ulcer ganic stenosis may have a high-grade retention of acid gastric con- without developing gastric ulcer.

he results of experiments on ligation of the blood vessels of the ch reveal the remarkable collateral circulation of the gastric mucosa. must be kept in mind in interpreting the negative results on the liga- f blood vessels in causing or delaying healing of gastric ulcer; it also be remembered that when the blood supply of the acid-forming sa is disturbed, the secretion of acid is decreased or abolished. How- when the blood supply is retarded, the mucosa becomes more

susceptible to the digestive action of acid-pepsin. The results might not have been so universally negative if it had been possible for the investigators to ligate the arterioles or venules in the submucosa. If the integrity of these vessels is seriously disturbed, then an erosion or an acute ulcer results.

Systemic infection is an important factor in the total picture of the pathogenesis of the duodenal (71 per cent) and gastric ulcers (21 per cent; 8 per cent both sites) which occur after an extensive skin burn. Congestion of the mucosa is the background for subsequent ulceration by the digestive juices. The systemic infection apparently acts by decreasing the general resistance which predisposes to the progression of the ulcer and not by producing the ulcer through a local infectious process. The predilection of the duodenum as a site is probably due to the fact that, given conditions which tax the resistance of the mucosa of the upper alimentary tract, the duodenum will succumb before the stomach.

Cinchophen causes ulcer to form preferentially on the lesser curvature near the pyloric outlet and less frequently in the duodenum. The original lesion is a diffuse or focal gastritis which occurs regardless of the route of administration; this leads to the formation of erosions, all of which finally heal except those which develop into ulcer in the preferential sites. These ulcers are prevented to a variable extent from occurring by section of the pyloric sphincter, the administration of large doses of Vitamin D, stilbesterol, gastric mucin, pectin, and alkalies.

Acute peptic ulcers may be produced by hetero- or auto-cytotoxin, by a local allergic reaction, or by a Shwartzman reaction, but such ulcers, unless they perforate, heal rapidly.

A protein and Vitamin B deficient diet has been associated with the occurrence of gastric and duodenal ulcers in several species of animals. A Vitamin C deficient diet leads to the occurrence of gastric ulcers in guinea pigs and a failure of acute lesions of the gastric mucosa to heal normally. In the chick, the lack of the anti-gizzard erosion factor causes gizzard erosions which are prevented by milk or cholic acid. The factor, the nature of which is unknown, is believed to promote the formation of cholic acid. Calcium deficiency causes ulcers of the glandular stomach of rats.

Definite acute or subacute ulcers of the duodenum occur occasionally in dogs which live for several days or weeks in a state of chronic adrenal insufficiency. Acute ulcers and erosions of the stomach and duodenum occur in thyroparathyroidectomized dogs which succumb within a few days to weeks after the operation; the same is true of animals after operation on the pituitary gland. Large doses of extracts (pressor fraction) of the posterior lobe of the hypophysis may cause acute lesions of the

omach in rats and rabbits. This is not true of dogs. The acute lesions sociated with acute insults of an endocrine nature would appear to be ue to vascular disturbances associated with the shock, hemoconcentra-on, or trauma of an operation or its sequelae, or to the rupture of blood ssels by spastic contractions of the gastric or intestinal musculature. he beneficial effect of pregnancy on peptic ulcer has not been clarified though it still holds much interest.

The incidence of jejunal ulcer in dogs after gastrojejunostomy varies dely among the various reports in the literature. The discrepancies may explained as due to length of observation after the operation, the uma to the jejunum with clamps, hematoma formation, the skill of the erator, and the extent to which the anastomosis was made distally m the beginning of the jejunum.

The spontaneous occurrence of jejunal ulcer in man and dog in from to 25 per cent of cases after gastrojejunostomy led to an extensive perimental study of the cause of this ulcer. It was found particularly Mann and Williamson that jejunal ulcer occurred in the dog quite iformly after a gastrojejunostomy when the alkaline pancreatic juice and e were drained into the last 15 cm. of ileum (internal duodenal drain-e). It has been shown unequivocally that this jejunal ulcer is due to the ceptibility of the jejunal mucosa to the corrosive action of acid gastric ntents. It has also been shown that the jejunal mucosa is more suscepti- than the duodenal mucosa to the development of ulcer when internal odenal drainage is performed and that if a soft, nutritious, easily estible diet is fed with raw ground liver and raw ground pancreas to vide digestive enzymes, the development of the ulcer is delayed but prevented. Thus, *nutrition* is a predisposing factor, but *acidity* of the tric contents and the *susceptibility* of the jejunal mucosa are the primary ors involved. When the acid factor is adequately controlled by surgical medical procedures, the ulcer does not occur.

There is no sound reason to question the conclusion that postoperative nal ulcer in man is due primarily to acid gastric contents bathing a cosa less resistant to acid-pepsin than the gastric and duodenal mucosa. nce, the counterpart of one type of human ulcer has been produced erimentally in the dog.

In the case of the postoperative jejunal ulcer, the ulcer arises from dequate defensive properties of the mucosa though in some cases the ressive factor— more prolonged acid secretion—is evident. Undoubt-, the ulcer produced in the dog by cinchophen is analogous to the r which occurs under the same conditions in man.

Cinchophen, by producing gastritis and duodenitis, decreases the nsive properties of the mucosa. A deficiency of protein and Vitamin B,

both important in growth, would impair the defensive properties
mucosa.

Hence, in these cases in which types of ulcers which occur in ma
been produced experimentally, the chief common factor respons
ulcer genesis is a decrease in the defensive properties of the mucosa

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study the development and treatment of peptic ulcer. Harper made the observation that when the pouch was constructed in the cardiac or in the pyloric region, no ulcers occurred in the fistula, and when two intestinal fistulas were made into the same fundic pouch, no ulcers occurred in either fistula until one of them was removed. Furthermore, in contrast to the observations of Matthews, it was noted that when ulcers were forming, the dog's general condition was poor; that is, there was anorexia,

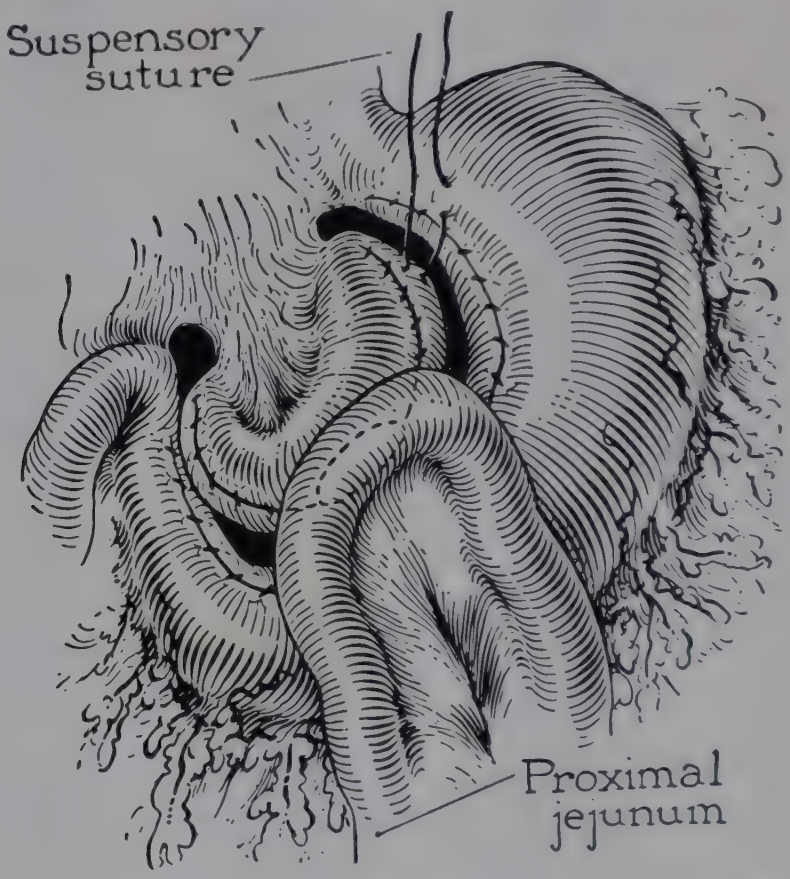


FIG. 72. A drawing showing the formation of a gastric pouch from the lesser curvature and anastomosis of a loop of the proximal jejunum. Note the suspensory suture to prevent the pouch from being pulled or stretched subsequently. (Courtesy, Gage et al.: *Arch. Surg.*, **10:** 10, 1936.)

vomiting, and loss of weight. The same finding was reported for pigs by Florey et al. (499). Harper's findings were confirmed by Kunlin and Cavalli (500). Palma (501), on the basis of nine experiments lasting up to 155 days, denied that fistulae into the fundus resulted in ulcers; he obtained ulcers of the intestinal segment in 77 per cent of his animals when the fistula was made in the pyloric antrum. This cannot, however, be construed as a contradiction of Harper, because Palma was not working with pouches.

Commenting on the relative infrequency of ulceration in Pavlov

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UTLINE OF CHAPTER 11

Relation of Nicotine, Alcohol, and Caffeine to Peptic Ulcer

I. NICOTINE

- A. INTRODUCTION
- B. EFFECT OF SMOKING ON THE FUNCTIONS OF THE STOMACH
  1. Motility
     a. Comment
  2. Secretion
     a. Fasting Secretion
     b. Stimulated Secretion
     c. Comment
- C. EFFECT OF NICOTINE ON THE GASTRIC MUCOSA
- D. COMMENT

I. ALCOHOL

I. CAFFEINE

- A. PRODUCTION OF EXPERIMENTAL ULCER BY CAFFEINE
- B. EFFECT OF CAFFEINE AND RELATED BEVERAGES ON GASTRIC SECRETION
  1. In the Dog
  2. In the Cat
  3. In Man
- C. COMMENT

. SUMMARY

CHAPTER 11

Relation of Nicotine, Alcohol, and Caffeine to Peptic Ulcer

Nicotine

Introduction

The effect of smoking on gastric function and on peptic ulcer is a subject of great importance, and yet it is confused by some of the poores observations and some of the wildest generalizations imaginable. Opinio varies from a belief that smoking may *cause* peptic ulcer to a convictio that smoking has nothing whatever to do with either the onset or th course of the disease. We (1) were stimulated to undertake our work o this subject when we could not find satisfactory evidence in the literatur upon which to base an opinion. As far as we could determine, the re viewers (2–5) had been content to accept any statements made, regardles of how poorly supported.

We are going to review the problem here because (a) it has not bee brought up to date in recent years, (b) it is desirable to distinguish clearl between the facts and the assumptions, and (c) we wish to encourag further investigations into this problem.

Effect of Smoking on the Functions of the Stomach

Motility. The first direct objective measurements of the effect o smoking on motility were made by Carlson and Lewis (6), who demon strated that the effect on hunger contractions in normal individuals wa consistently inhibitory. A cigarette or mild cigar caused only slight inhibi tion, while a strong cigar or pipe caused complete and prolonged inhibi tion. The latter observation was confirmed (7). We do not know of an published kymographic studies of the effect of smoking on the gastri motility in ulcer patients. In unpublished studies Pollard (8) has re peatedly tested the effect on these patients of smoking during periods o quiescence of the stomach; he has not observed that motility is stimulate under these conditions. The patients were in all instances habitual smoker

Fluoroscopic findings during or after smoking are conflicting (9–1

), which is not surprising considering how inadequately most of the idies were conducted. For example, Gray (11) concluded that in duonal ulcer patients "peristalsis was generally increased when smoking as allowed prior to the administration of the barium meal." This nclusion was based on the finding that in the control fluoroscopy 62 per nt of the 50 patients had increased peristalsis; whereas after smoking, per cent had increased peristalsis.

Emptying time has generally been found to be unaffected by smoking, gardless of whether an ulcer was present or not (1, 9, 11).

Comment. We (1) found that the hunger contractions of the stomach man cease after the first few puffs of smoke. The hunger contractions, en inhibited by smoking one cigarette, may not recur for from 15 to minutes after cessation of smoking. We did not observe that a period augmented motility precedes the inhibition, as claimed by Danielopolu al. (7).

The promptness with which the contractions are inhibited was interted by Carlson as indicating a reflex inhibition, rather than a nicotine ion. We (1) identified the motor pathway for this inhibition as follows: e subcutaneous injection of 1 mg. of nicotine into well-trained unanestized dogs did not inhibit the hunger contractions, but the inhalation cigarette smoke by well-trained dogs inhibited hunger contractions mptly. Inhibition also occurred following inhalation of the smoke in ee dogs which had undergone celiac ganglionectomy and splanchotomy, but not in dogs with supradiaphragmatic vagotomy. These eriments prove that in the dog tobacco smoke inhibits hunger conctions through a reflex mechanism, and the efferent side of the reflex is in the vagi. The evidence also shows that ordinary amounts of otine do not produce gastric motor effects by acting directly on the al gastric ganglia, by raising the blood sugar, or by causing a discharge drenalin. It does not follow, however, that all of the effects of smoking the digestive tract are mediated by a single mechanism.

In our experiments, the smoking of from three to four cigarettes during hour by normal smokers or by patients with duodenal ulcer usually not delay the emptying of a test-meal from the stomach. When any ct was observed, it was in the direction of an inhibition of gastric cuation. Dickson and Wilson (16) observed a slight decrease in gastric ility in four subjects when several pipes or cigarettes were smoked before or during the evacuation of a barium sulfate meal. Of course, tendency toward reduced gastric motility and toward retention may xaggerated when solid food is ingested, but we have not performed riments to determine the truth of such an assumption.

SECRETION. The earliest experiments are of historic interest only Wolff (12), in 1889, performed a few tests on the effect of introducin 1 mg. of nicotine into the stomach along with a meal. He detected n consistent effect, but acknowledged that his observations were too limite and his methods too crude to permit any conclusions. In 1909, Skaller (13 went to extremes to demonstrate an effect of smoking on gastric secretion He aspirated the smoke of a cigar or of several cigarettes through 20 cc of water, then injected this material into Pavlov or Heidenhain pouc dogs. After a latent period of from one to three hours, which was appar ently the time it took these dogs to get over the severe toxic effects, ther was an increased volume of secretion. Whether this juice had any acidit was not determined. It is interesting that up to the late 1920's, althoug the hypersecretory and hyperperistaltic effects of smoking had come to b taken for granted, the above were the only experiments on record. As fa as we can determine, it was about 20 years before a further attempt wa made to obtain objective evidence on this point.

Fasting Secretion. Gray (11) concluded that "fifty patients with duoden ulcer showed an increase in gastric secretion and acidity if they smoke on a fasting stomach," but the basis for this conclusion is not apparen from his data. Friedrich (14) aspirated the fasting gastric contents a intervals of 10 minutes for one hour in 17 cases of duodenal ulcer, and o a subsequent occasion repeated the aspirations with the patient smokin He observed an increase in volume, or acidity, or both, in all case Rosenblum (15) measured the volume and acidity of the residuum (ulcer patients; he then returned all except 10 cc. of this residuum and ha the patients smoke one cigarette. After 20 minutes, the stomach wa emptied and 50 cc. of 7 per cent alcohol introduced. Twenty minute later a sample was aspirated for an acidity determination. The design (this experiment is not entirely clear to us. Control procedures should hav been carried out in exactly the same way in the same group of ulcer pa tients with omission of the smoking, instead of using as controls 18 nor ulcer patients, 14 of whom were women. At any rate, Rosenblum conclude that smoking increases the volume and acidity of fasting gastric juice i both ulcer and non-ulcer patients.

Stimulated Secretion. Gray (11) studied the effect of smoking on th gastric secretory response to a test-meal. Instead of showing figures t indicate how the acidity in a given individual was affected by smokin he merely enumerated the number of patients who had hyperacidit when not smoking as compared with smoking. He did not indicate wha he classed as hyperacidity, or how many determinations were made. I short, his data are such as to make an appraisal of his findings impossibl Ehrenfeld and Sturtevant (17) demonstrated that the curve of respon

alcohol is from 10 to 15 units higher in both normal and ulcer patients
er smoking two cigarettes.

Comment. We (1) have studied the effect of smoking from four to seven
garettes over a period of one hour and 50 minutes on the fasting secretion
25 smokers, 15 nonsmokers and 20 patients with duodenal ulcer. The
sting contents were removed with a Rehfuss tube, and the subjects were
ld to expectorate all saliva. The basal secretion for four 10 minute
riods was determined by continuous aspiration, and then smoking was
arted; the volume of secretion obtained every 10 minutes was recorded
d the acidity titrated. This was repeated at least twice and usually three
nes on each subject.

In only one of the 40 normal subjects were the volume and acidity
the fasting secretion augmented. In 17 of the 40, no statistically sig-
ficant change occurred, while in 22 an appreciable decrease in volume
d acidity resulted.

In only one of the 20 patients with ulcer (a nonsmoker) did any sig-
icant increase in gastric acidity of the basal secretion result; eight
owed no significant change; 11 showed a decrease in acidity.

These tests were repeated on six chronic smokers and six nonsmokers
o were told to swallow their saliva. On smoking, either no change or
light decrease in acidity resulted.

The effects of smoking on the fasting secretion of dogs was studied by
ving four Pavlov pouch dogs smoke through a small trocar inserted
o the trachea under local anesthesia. The smoking of two cigarettes in
hour was accompanied by a slight depression of the volume and
dity. We also perfused 50 cc. of water through which the smoke of two
arettes had been drawn through a total pouch of the stomach. No
nulation of acid secretion occurred, although an increase in the pro-
tion of mucus was noted; nor was gastric secretion stimulated when a
ilar solution was introduced into the intestine of the total pouch dog.
en the smoke of four cigarettes was used, some of the dogs vomited,
night be expected, and the secretion of acid was depressed.

When nicotine was given subcutaneously to fasting dogs with gastric
ches in a dose of 0.2, 0.4, or 1.0 mg., equivalent to the nicotine ab-
ed from the smoke of one, two, or five cigarettes, the acid production
er did not change or decreased. In numerous experiments of this type,
stimulation was observed.

Similar observations were made regarding the effect of smoking on
response to a test-meal of 250 cc. of beef tea and three crackers. In
non-ulcer group, the acidity was sufficiently diminished in three of
four subjects that the average for the group was lowered. In the ulcer
ents, no change occurred (Table 15). Furthermore, the response of

Pavlov pouch dogs to a standard meal was unaffected in two instance and slightly depressed in a third by the subcutaneous injection of 1 mg. of nicotine.

Table 15

EFFECT OF SMOKING ON THE ACIDITY OF THE GASTRIC CONTENTS IN RESPONSE TO TEST-MEAL IN HABITUAL SMOKERS

Subjects	*Control*			*Smoking 3 or 4 Cigarettes*		
	Vol.	*Acidity, Cl. U.*		*Vol.*	*Acidity, Cl. U.*	
		Free	*Total*		*Free*	*Total*
Non-ulcer (7)	63	33	54	67	20	37
Ulcer (22)	92	52	62	92	50	61

EFFECT OF NICOTINE ON THE GASTRIC MUCOSA

The experiments reported involved the use of toxic doses of the dru Grosmann and Jiano (18) reported that in chronic nicotine poisoning dogs, changes occur in the interstitial tissue of the gastric glands and the chief and parietal cells. Curiously, they made no mention of the gro appearance of the mucosa. In acute and chronic experiments, Weselma (19) studied the effects of large intravenous doses of nicotine in do Direct observation of the gastric mucosa revealed that for the first thr minutes after an injection of the drug, there was a distinct pallor: th passed over into a diffuse hyperemia lasting about seven minutes, follow by an irregular dissipation of the hyperemia, which gave a patchy appea ance to the mucosa. The mechanism was considered to be one of "veget tive irritation," predominantly vagal, causing a vasoconstriction. In t chronic experiments, hemorrhagic erosions were reported.

COMMENT

Crämer (20) became interested in the adverse effects of tobacco digestion as a result of personal experience. He had been suffering fro dyspepsia, eructation, flatulence, anorexia, and spastic colon for so time; he was only a moderate cigar smoker, but gradually he found th smoking was becoming distasteful and eventually he stopped altogeth Amazed at the prompt improvement which took place in his sympton he concluded that he had been suffering from chronic nicotine poisoni Thereafter, Cramer wrote a great deal about the effects of nicotine digestion; he was apparently the first to attribute to smoking an etiolo

e in peptic ulcer, a view to which others (21, 22) also subscribed. So far we can determine, the only objective experiments which any of these nicians performed were to add some nicotine to gastric juice and show t digestion was inhibited. This might conceivably predispose to spepsia in tobacco chewers, but how it would aggravate a duodenal or tric ulcer in a smoker is not clear. On the contrary, an inhibition of ptic digestion would be a salutary effect in peptic ulcer, although it is ubtful if enough nicotine ever reached the stomach to make the *in vitro* periments of any significance. For example, Lickint (2) found that the iva of smokers inhibited peptic digestion only if it was collected during d shortly after smoking.

The kind of observation upon which the views of Crämer and others re based were that in 75 per cent of hypersecretors there was a history abuse of tobacco; or that smoking could cause a symptom complex ical of duodenal ulcer (23); or that pyrosis was a complaint of 75 per t of smokers*; or that there was a great increase of duodenal ulcer ring and after World War I concomitant with a great increase in oking; consequently, smoking was causing the ulcer. And throughout se discussions, the ever recurring theme was that smoking causes perperistalsis and hypersecretion, although no experiments to demonte this phenomenon in humans were reported until the middle 1920's. other words, it appears to have been one of those medical rumors ch everyone kept repeating under the impression that it was a proven . Even as late as 1938, Crohn (24) stated: "That tobacco, particularly he form of cigarettes, increases gastric secretion and produces acid ersecretion and pylorospasm has been shown experimentally and can demonstrated in any Rehfuss test-meal experiment." In our opinion, acid hypersecretion has not been shown experimentally to result from king and, in our experience, it is demonstrable only in an occasional vidual.

Meanwhile, the problem was rendered more confusing by other reports observations. For example, there were some who believed that the ts of smoking resulted only from the use of cigarettes, not cigars or r forms of tobacco. Adler (10), for instance, stated that the syndrome so specifically limited that he designated it "cigarette stomach." ording to Cramer (3), prolonged use of tobacco, especially chewing cco, eventually leads to achylia; and the "war-gastritis" which ted from excessive smoking was usually characterized by anacidity. has been confirmed by a survey made in northern Sweden, where

If true, then there has been a marked change in this symptom, because Short et al. obtained a history of pyrosis in only 1.2 per cent of 1300 smokers. Perhaps the y of the tobacco or its moisture content could explain the difference.

gastric secretory studies were made on a large group of the populatio
Anacidity was significantly more frequent among the snuff chewers (75
Hurst (25) considered smoking a factor in duodenal ulcer, much less so i
gastric ulcer. It did not appear to him that inhaling the smoke was essenti
to the adverse effect of smoking on duodenal ulcer, but Trowell (2
pointed out that the practice of inhaling is twice as common in duoden
ulcer patients as in normals. He also found that among smokers signif
cantly more ulcer patients inhale than do non-ulcer patients. This findin
has been supported by the results of a more recent study (76). Ulc
patients who smoke cigarettes or a pipe were compared as regards seve
and mild symptoms of ulcer. Significantly, ulcer patients who smok
cigarettes heavily had more severe symptoms than pipe smokers; pi
smokers as a rule do not inhale. Thus, it would appear that chewi
tobacco tends to produce a gastritis and anacidity and that heavy cigaret
smoking increases the severity of the symptoms of a significant number
ulcer patients. However, it has not been demonstrated why heavy i
halation of smoke enhances the symptoms and prevents remissions
good management, particularly in some patients.

We undertook our work with the hope that a single test of gast
function might determine objectively which ulcer patients should n
smoke or why smoking irritated the ulcer. This aim was not attained
our methods. In Pollard's (8) experience cigarette smoking did n
significantly increase the fasting gastric secretion nor did it stimulate co
tractions of the empty stomach in a large series of ulcer patients. Howeve
further studies are indicated because one cannot ignore the clinical o
servation that some ulcer patients appear to be improved by avoidi
tobacco, either in pursuance of the doctor's instructions or on their ow
initiative.

Statistical studies (27, 28) which minimize or negate smoking as
factor in aggravating ulcer symptoms or digestive complaints should n
be taken too seriously. Even though it may be true that the proporti
of smokers among ulcer patients is no greater than the proportion
smokers in the population at large, it is still possible that some ulc
patients are particularly susceptible to the effects of smoking.

This attitude is supported by a recent report (77) in which it w
found in a well-designed study that smoking decreases the effectiveness
the antacid management of the peptic ulcer patient. Fifty-six patie
who continued to smoke showed a favorable response to management
only 46.8 per cent of cases and 39 patients who had never smoked show
a favorable response in 85 per cent of cases. Twenty-six patients w
stopped smoking of their own accord responded to therapy and show
an incidence of 11.5 per cent recurrences, whereas 11 of 13 patie

no started smoking again showed a recurrence of the disease almost mediately.

Just how these effects are mediated is yet to be determined. In our periments, we obtained evidence that the amount of nicotine absorbed om two or three cigarettes does not produce any of the phenomena hich are reported to occur in those whose digestion is impaired by oking. In agreement with others (11, 17, 18, 29), we found no signifi- nt difference between ordinary cigarettes and "denicotinized" cigarettes. has been reported (11, 30) that no "sensitivity" to nicotine is demon- able in ulcer patients by skin tests.

The experiments on the effects of nicotine on the gastric mucosa are no help because of the great divergence between the amount of nicotine ministered and the amount absorbed even by "chain" smoking. oreover, the results are at variance with direct observations in a human bject (31), in whom the motor and secretory activity of the stomach d the color of the mucosa were unaltered by pleasurable smoking of a pe or cigarette. When the subject had no taste for smoking and was ghtly nauseated by it, the mucosa was moderately pale, and motility d secretion were diminished. Carefully conducted experiments have own that the smoking of cigarettes markedly reduces the flow of blood the extremities of human subjects. The effect of smoking on the blood w through the gastric mucosa needs careful study by refined methods.

Alcohol

Alcohol is almost uniformly interdicted in the management of peptic er because it is an irritant and stimulates gastric secretion. However, e, as in smoking, the experimental evidence to substantiate the clinical pressions that it plays a role in pathogenesis is not available.

The older literature on the effects of alcohol in relation to the patho- esis of peptic ulcer is reviewed by Redwitz and Fuss (78). The more nt literature on the influence of alcohol on the digestive tract has been iewed by us (71).

Certain physiologic effects of alcohol are clearly established. Alcohol nulates gastric secretion when given orally, rectally, or intravenously. y cc. of 7 per cent alcohol is a frequently used stimulant in gastric lysis. Higher concentrations (10 to 15 per cent) stimulate the produc- of mucus, which is considered evidence of irritation.

Large amounts of highly concentrated alcohol in man cause an acute ritis with achlorhydria, recovery from which is relatively rapid. In centrations of 30 per cent and over, alcohol produces desquamation ne surface epithelium in sheets or ranks (see p. 62).

About 50 per cent of chronic alcoholics have chronic gastritis upon

gastroscopic inspection (36), but there is no evidence that the incidence gastric or duodenal ulcer is increased in these persons.

The primary role of alcohol as the etiologic agent of chronic gastr is not entirely substantiated. The role of associated nutritional deficien in chronic gastritis has not been assessed. Probably both factors involved.

We have been unable to produce ulcers of the stomach or duoden in animals by giving them what would be equivalent to a quart of wh daily for a man (see p. 262).

The potentiation of gastric secretion by alcohol and tobacco has been confirmed by us. However, as is pointed out in the next sect alcohol potentiates caffeine.

Dragstedt (41) et al. have called attention to the similarities betw alcohol and histamine as stimulants of gastric secretion, and sugge the possibility that alcohol stimulates gastric secretion by the prim liberation of histamine.

Clinical evidence that use of alcohol is of etiologic significance in genesis of peptic ulcer is difficult to obtain, especially since the rol both acute and chronic gastritis in peptic ulcer is still a moot probl The evidence on drinking habits as reviewed by Redwitz and Fuss led them to conclude that a role for alcohol in the pathogenesis of u was not proved. There is slight evidence that alcohol may play an exc tory role in the recurrence of ulcer in some individuals.

Caffeine

Whereas smoking and the use of alcohol have been interdicted in management of peptic ulcer patients for many years, the consumptio caffeine-containing beverages has not, as a rule, been restricted ex during the early phase of treatment of the active ulcer. The relatio caffeine to ulcer and gastric secretion has not, until recently, been appreciated, mainly because in the past the subject has not been stu adequately.

Production of Experimental Ulcer by Caffeine

Hanke (33) demonstrated that the subcutaneous injection of doses of an aqueous solution of caffeine sodium salicylate was capa producing an acute erosive gastritis in cats. The stomachs contained contents which Hanke attributed to the caffeine. He offered these as evidence of acid gastric juice producing "peptic" lesions. Hanke also succeeded in producing "chronic gastric ulcers" by the daily cutaneous injection of 200 to 300 mgs. of caffeine sodium salicylate

ods up to 60 days. However, close examination of his photomicro-phs reveals only superficial desquamation of the surface and glandular helium; these erosions were located chiefly in the corpus, but also he pyloric region. He did not perform control experiments using um salicylate, which in itself is capable of producing lesions in the ric mucosa (35).

Molteni (37) produced erosive and ulcerative lesions in the antrum pylorus of 40 per cent of rats by the daily subcutaneous injection of 30 mg. of caffeine sodium salicylate over a period of time varying 10 to 70 days. In another series of rats, injected with caffeine daily 0 days, the dose was stopped and the animals sacrificed at eight, 15, 20 days. In this group, no ulcerations were found and Molteni con-ed that the lesions heal rapidly. He also found more acid and a larger me of gastric contents in the stomachs of test animals than in the rols (water injections). This, he concluded, was evidence that hyper-tion of an acid gastric juice was an important factor in the patho-sis of ulcers produced by caffeine. However, this investigator also l to control his experiments with regard to the salicylate.

udd (38) used caffeine in a mixture of beeswax and mineral oil ar to the one used in the production of "histamine ulcers" (p. 213) obtained ulcers in 40 per cent of guinea pigs and cats. The guinea were injected daily with 100 mg. of caffeine (alkaloid), intramuscu-and developed ulcers in an average of 4.5 days. The cats received ng. of caffeine daily and developed ulcers in an average time of days. The ulcers were for the most part gastric in location. There one associated duodenal ulcer and one duodenal ulcer without a c lesion. He too suspected the mechanism was the constant elabora-of an excessively acid gastric juice. We (39) confirmed the work of and reported additional observations which may explain in part the genesis of caffeine-induced ulcers (40).

irect observation of a mucosal stoma in the cat shows a persistent ing (hyperemia) followed by cyanosis after the intravenous adminis-n of caffeine. Microscopic sections, made at the time when the sa grossly appeared more reddened, thicker, and succulent, showed ent dilatation and engorgement of veins and venules of the sub-sa. However, when the mucosa appeared cyanotic, there was pro-ced dilatation and engorgement of the mucosal venules. Continuous eated stimulation of gastric secretion in the anesthetized cat with nine for 10 to 12 hours produces no apparent change in the gastric sa. But if caffeine (125 mg. intravenously or by direct lavage of the ch for 30 minutes) is alternated with the histamine (0.3 mg.), large e areas of epithelial desquamation and multiple bleeding erosions

and ulcerations of the gastric mucosa are observed in as short a time a five hours.

Effect of Caffeine and Related Beverages on Gastric Secretion

The earliest attempt to study the effect of caffeine upon gastric secre tions was made by Wolff (12) in 1889. He used caffeine in doses of 200 t 300 mg. in combination with the usual Ewald test-meal and concluded on the basis of his study of three subjects, that caffeine reduced the tota acidity of the gastric contents.

In the Dog. Studies on gastric secretion with caffeine in the dog hav been consistently negative. Various investigators (38, 42–48), have foun that caffeine administered orally or intravenously to Pavlov and Heide hain pouch dogs has no influence upon gastric secretion. However, sever authors (43, 45, 49–51) observed a stimulation of gastric secretion whe decoctions of coffee and decaffeinated coffee were given via the stomac tube to Pavlov pouch and duodenal fistula dogs. The discrepancy led to search for some secretory agent in coffee other than caffeine.

Eweyk and Tennenbaum (52) found that certain protein substanc which had no secretory effect acquired stimulatory properties upo roasting to 140° C. They believed that this secretory activity depende upon the formation of histamine. Infusions of roasted corn (50) and brea crust (53) have been shown to stimulate gastric secretion. Bickel (49, 5 assumed that the protein components of the coffee bean were transform into histamine during the roasting process and the latter was responsib for stimulating gastric secretion. Bleyer et al. (54) agree that histami is the active substance in the roasted product. In a recent review of t pharmacologic activity of caffeine and coffee, Eichler (55) concludes th most of the evidence supports the "roast product." He argued that a stimulating effect from caffeine was the result of a central action.

If histamine is formed in the process of roasting, it would be wort of investigation to determine whether or not sufficient histamine is pres in ordinary quantities of coffee used to stimulate gastric secretion wh administered by the oral route. Experiments in this laboratory (56) ha shown that histamine in doses of 10 to 25 mg. must be used to be effecti orally.

We (58) were unable to elicit any secretion in dogs with doses up 250 mg. of the alkaloid, but Merendino et al. (57) reported a mark rise in the acidity and volume following the injection of 2500 mg. caffeine alkaloid in beeswax daily for four consecutive days. Recently (74) have found that caffeine markedly increases the gastric secret response to histamine in the dog.

In the Cat. We (58) demonstrated that the intravenous injection of feine in anesthetized cats provokes a marked stimulation of gastric retion. The latent period averages about 12 minutes and the duration increased secretion is approximately 45 minutes.

In Man. Considerable disagreement is found in the literature con-ning the effect of caffeine upon gastric secretions in *man*. The literature the effect of caffeine and related beverages in man will best be reviewed ether because of the close relationship of their investigation.

Miller et al. (59) reported that the addition of a liter of coffee to a -meal (beefsteak, potato, bread and butter) produced no delay in the ptying time of the stomach and did not appreciably affect the secretory ponse to the test-meal. One would not expect to learn much about the ct of coffee in the presence of such a test-meal.

Comparing the response in 15 normal human subjects to 300 cc. water, cc. 5 per cent alcohol, and 300 cc. water with 200 mg. caffeine, on cessive days, Goldbloom (46) found that 80 per cent showed stimulation n water alone, 100 per cent from alcohol, but only 50 per cent from caffeine solution. However, he made an analysis for volume and lity on a single specimen of gastric contents withdrawn at an interval 5 minutes after introducing the test solutions. His failure to obtain a her percentage of stimulation can be explained in view of the fact that have found the peak of the caffeine secretory curve to appear at 35 to minutes. Ehrmann and Dinkin (60) reported that caffeine does not ulate gastric secretion in human subjects any more than a pure water -meal. Their comparison is not legitimate in that they gave the water ly and the caffeine parenterally as the soluble sodium salicylate salt.

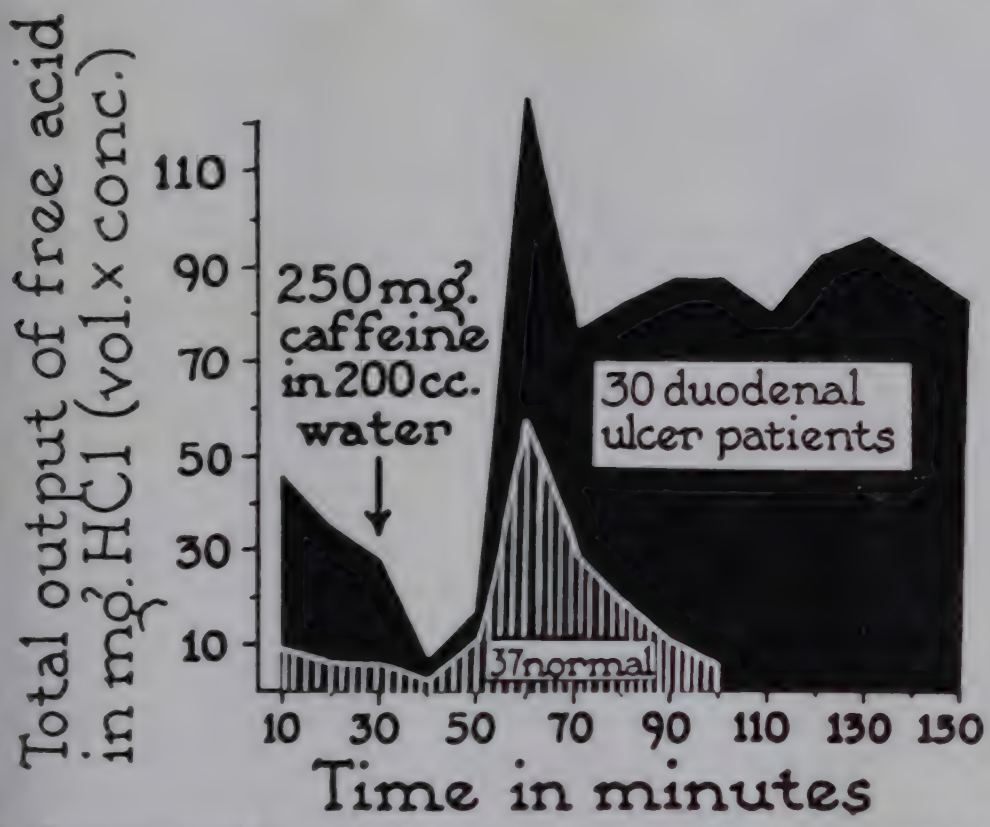
Ohnell and Berg (61) found only slight differences between the acidity es after infusions of crude coffee, roasted coffee, and roasted Kaffee (decaffeinated) on human subjects and concluded that "the essenti-active substance is not caffeine, nor is it likely to be a product derived the roasting process." On the basis of these studies, it would appear a secretagogue was present in crude coffee as well as the roasted luct, whether decaffeinated or not. However, these results are not ence against the excitosecretory effect of caffeine in man, nor do they rove the possibility that a secretagogue is formed in the process of ting. It is conceivable that the roasting process may also destroy secretagogue present in the green coffee bean, and the process of ffeination may produce or introduce an extractable substance which pable of stimulating gastric secretion. In analyzing the curves obtained heir ulcer patients, it appears to us that the ulcer patients showed a prolonged response than the normal subjects; however, Ohnell and made no such comment or interpretation.

Haneborg (62) gave two human subjects 500 cc. of a 6 per cent coffe infusion and found an elevated acidity which was significantly above th after water, but not quite as strong as after bouillon. Kaffee Hag produce no higher acidity than pure water, but the addition of 300 to 500 mg caffeine resulted in an elevation of the acidity. Katsch and Kalk (6 compared alcohol and caffeine test-meals on normal human subjects an observed a less abundant volume of secretion after the caffeine (200 mg in 300 cc. water), but a higher level of acidity than after alcohol (300 cc 5 per cent). The stomach emptied faster after caffeine than after alcoho They also obtained a stimulation of gastric secretion by the intraveno administration of caffeine. Haller and Bloch (64) reported that th caffeine test-meal gave higher acid values than water in their group normal human subjects. Cade and Milhaud (65) studied the response to caffeine test-meal in various patients. Seventy per cent of a series patients with gastroduodenal ulcers showed acid values higher than tho of their controls. In all cases of gastric carcinoma, except one, there w an achlorhydria to caffeine. Varying the dose of the caffeine (30, 60, a 100 mg.), they observed the highest secretory response to 100 mg. their normal subjects. The most accurately controlled fractional gast analyses, using caffeine as a stimulant of gastric secretion, were report by Wichels (66). He found that caffeine administered orally, intradu denally, or intramuscularly provoked a copious flow of acid gastric juic In spite of this evidence, the most recent reviewer of the subject (5 concluded that caffeine did not have a direct stimulating effect up gastric secretion and that the "roast product," most likely histamine, w the responsible agent in coffee.

We (67) studied the gastric secretory response to caffeine and caffeine-containing and substitute beverages in normal subjects and pep ulcer patients. Caffeine was administered as the sodium benzoate, 0.5 g in 200 cc. of water being introduced via stomach tube after removal of fasting residuum and aspiration of the continuous secretion every minutes for 30 minutes.

In the 50 normal or asymptomatic subjects, three types of respon were obtained. Seventy-five per cent showed an abrupt transient stimu tion followed by a return to the control level within 60 to 75 minutes. 15 per cent, a low flat curve was obtained which returned to the con level in 70 to 80 minutes. The remaining 10 per cent (five subje showed a prolonged secretory response. It is noteworthy that three of th five individuals subsequently developed epigastric distress simula ulcer, and in one a prepyloric ulcer was found by x-ray.

Of the 36 ulcer patients studied, 30 had proved duodenal ulcer six gastric ulcer. With one exception, all of these patients consiste



91. Comparison of the gastric secretory response of normal persons and ulcer patients to a caffeine test meal.

ved a prolonged response to the caffeine solution (Fig. 91). Gastric r patients manifested a lower peak response and a greater tendency to rn toward the control level at the end of two hours than did the duo- al ulcer patients.

t was further demonstrated (68) that caffeine acts synergistically with mine or alcohol. The administration of both caffeine and histamine normal individual results in a high prolonged curve similar to that h is produced in the ulcer patient by the administration of caffeine e. If the ulcer patient produces histamine, and since caffeine and mine act synergistically, this would explain the prolonged response e ulcer patient to caffeine.

After studying the gastric secretory response to pure caffeine, our tion was directed to the practical problem of the effect of various ine-containing beverages and substitute beverages. The preparations d and the average free acid response in normal individuals (the same ubjects were used in each experiment) is shown in Fig. 92. Although ka" contains relatively little caffeine, it provokes considerable ulation of gastric secretion, presumably because of its content of other tagogues.

he average total output curves in response to 300 cc. (about two cups) ffee in normal subjects and in duodenal ulcer patients are compared g. 93. It is obvious that coffee produces a more elevated and more

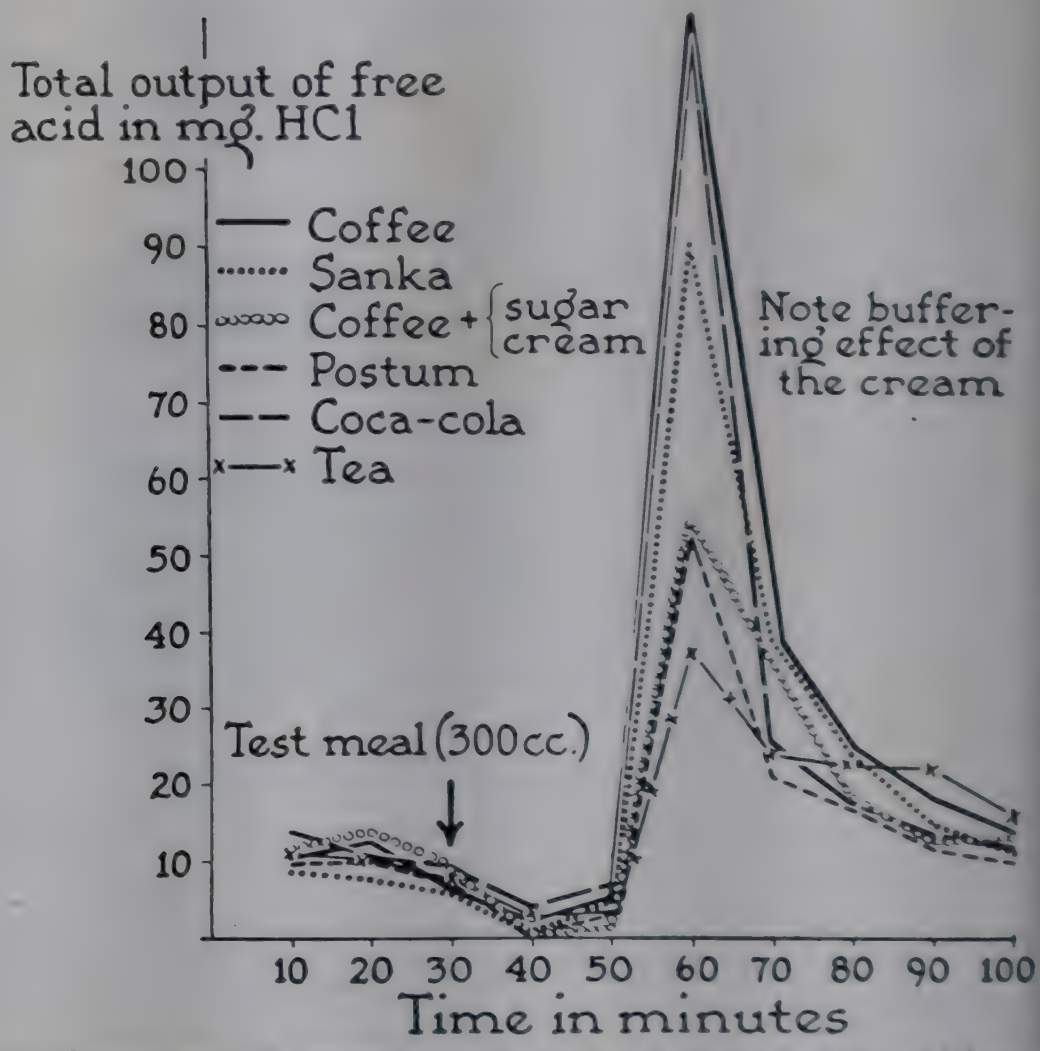


FIG. 92. Comparison of average gastric secretory response produced by va beverages. The same group of subjects was used for all the beverages.

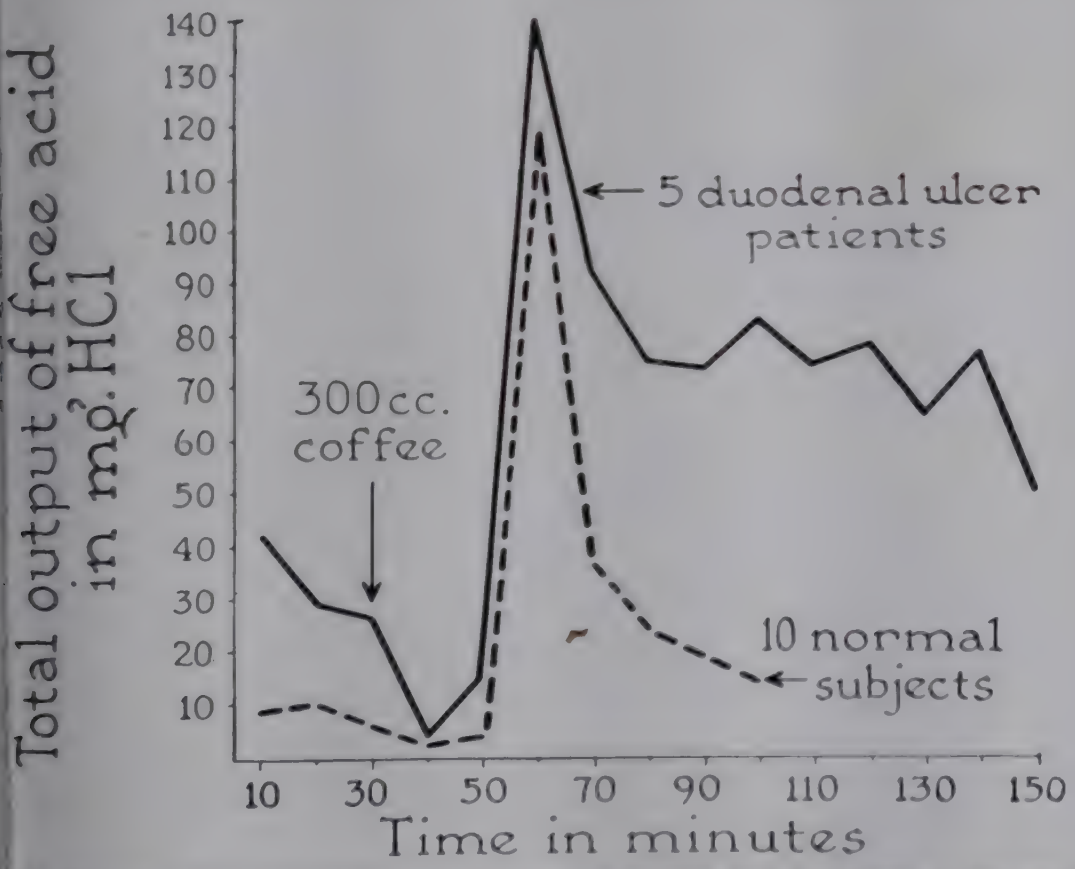
prolonged secretion in the ulcer-bearing individual than in the normal

In a survey made in northern Sweden (75) on a relatively l number of persons with and without peptic ulcer, it was found that incidence of heavy coffee drinking was significantly higher among pat with ulcer. In a group of 532 persons 17 of 60 (28 per cent) who d more than eight cups of coffee daily had an ulcer, and only 85 of (17.5 per cent) who drank less than eight cups a day had an ulcer. difference between 28 and 17.5 per cent is statistically significant.

COMMENT

Not all students of the problem are in accord regarding the signifi of the experiments and clinical observations just reviewed. It is a that (a) peptic ulcer may be produced in cats or guinea pigs in a rela short period of time by the prolonged and continuous administrati caffeine alkaloid in beeswax; (b) caffeine is a moderately potent stim of gastric secretion when administered orally, intramuscularly, or i

ously to man or the cat; and (c) a majority of patients with active roduodenal ulcer manifest a prolonged and sustained increase in the l output of free hydrochloric acid in response to the caffeine test-meal. However, the following questions have provoked differences of opinion: Are the experimentally induced ulcers in cats or guinea pigs attutable solely to caffeine "intoxication" or to other pharmacodynamic cts of the continuous administration of the drug? (b) Does the excessive sumption of caffeine-containing beverages produce peptic ulcer in n? We do not propose that caffeine causes ulcer in man, but believe asonable to suggest, on the basis of the evidence reviewed, that the y consumption of 10 to 15 cups of coffee over a long time may conute to the pathogenesis of ulcer in the individual with the associated hesis or substrate. (c) Do *all* ulcer patients respond to caffeine stimula- by a prolonged and sustained increase in the total output of free rochloric acid? (d) Does caffeine stimulate gastric secretion in the dog? Giddings et al. (69) objected to the mode of administration of caffeine l by Judd (38) and by us (39) in the production of ulcers, namely, the amuscular implantation in the beeswax and mineral oil mixture. They oned that "the effect produced under these conditions might be rent from that obtained with the more rapid absorption and the



03. Gastric secretory response of normal persons and duodenal ulcer patients to 300 cc. of black coffee.

action of shorter duration that occur when caffeine is taken by mouth. For precisely this reason, caffeine was embedded in a beeswax and mineral oil mixture in an attempt to obtain the prolonged action of caffeine through its slow liberation and gradual absorption. It is granted that this mode of administration is not the normal route for human consumption of caffeine.

Giddings et al. recently reported (69) that "ulcers were produced in cats by caffeine only when the doses were large enough to kill the animal and attributed the pathogenesis of these ulcers to "toxicity." The authors conducted experiments which demonstrated the upper limit at which caffeine (aqueous) can be administered orally without causing death in cats (75 to 100 mg. per kg.) and confirmed the conclusions regarding the lethal dose drawn by Salant (70). Because the dose of caffeine in beeswax (85 to 190 mg. per kg.) used by us and by Judd exceeded this amount in some instances, Giddings et al. concluded that this was a "toxic" dose. Toxicity depends not only upon the absolute dose of a drug but also the route of administration and rate of absorption. The experiments devised to determine toxicity and lethal dose were based on a rapidly absorbed and administered preparation of caffeine (aqueous) and therefore one is not justified in drawing direct conclusions regarding size of dose when the drug is given in a different vehicle (beeswax) which releases it slowly for absorption.

Just what constitutes "toxicity" in the case of caffeine? This question cannot be definitely answered with existing knowledge. It has been shown (39) that continuous or repeated stimulation of gastric secretion in the anesthetized cat with histamine for 10 or 12 hours produced no apparent change in the gastric mucosa. But, if caffeine intravenously or by direct lavage of the stomach was alternated with the histamine, large diffuse areas of epithelial desquamation, multiple bleeding erosions, and ulcerations of the gastric mucosa were observed in as short a time as five to seven hours. Since both caffeine and histamine stimulate the flow of acid gastric juice and cause vasodilatation, and since histamine alone does not induce ulceration of the gastric mucosa in acute experiments, it is caffeine presumably provides an additional factor which contributes to the decreased resistance of the mucosa. This alteration in the susceptibility of the gastric mucosa to the proteolytic action of gastric juice has been arbitrarily designated and attributed to "cellular toxicity." This factor may involve alteration in cell permeability, the concept of caffeine-histamine synergism, or a more prolonged stimulation of pepsin than is provoked by histamine.

Giddings et al. attempted to translate directly from the dose of caf

equired to produce ulcers in cats to that theoretically necessary in man n the basis of body weight (28 times), and arrived at an enormous uantity of coffee. Such comparisons are not reliable when we consider ne relationship of the doses necessary to stimulate gastric secretion in ne cat (65 to 125 mg.) and man (80 to 250 mg.). In the secretory experi- nents, the average stimulating dose on a body weight basis in the cat is pproximately 13 times greater than that in man. The amount of caffeine sed to produce ulcers (300 mg.) was relatively large, to be sure, but it nust be remembered that the experiments were set up to produce ulcers n a relatively short period of time in a species of animal that does not pontaneously develop gastroduodenal ulcers.

In addition to the above direct pharmacodynamic effects of caffeine pon the stomach, there may or may not be a neurogenic factor by virtue the excitatory action of caffeine upon the central nervous system.

Caffeine may aggravate an already existing ulcer in much the same anner as do alcohol, smoking, food indiscretions, etc. For these reasons, e believe the consumption of caffeine-containing beverages should be nterdicted in the management of the gastroduodenal ulcer patient: a) caffeine is capable of producing ulcers in cats and guinea pigs; (b) affeine provokes a prolonged and sustained stimulation of both the acid nd pepsin secretion in the majority of ulcer patients; (c) coffee induced aggravated the symptomatic distress in 70 per cent of one series of cer patients; (d) caffeine produces vascular changes in the gastric ucosa of the cat which are similar to those induced by prolonged resent- ent, hostility, and anxiety, and which appear to render the mucosa more sceptible to erosion. Whether or not complete abstinence is recom- ended to the patient depends on the individual's reaction to total stinence. The latter in some instances may be more aggravating to e ulcer than the pharmacodynamic effects of caffeine and in such a uation a compromise restriction in the quantity of coffee (or coca cola) ith the use of sugar and cream would seem wise.

Do all ulcer patients respond to the caffeine test-meal by a prolonged nd sustained increase in the total output of free hydrochloric acid? In our iginal studies (67), one patient out of 36 did not have the above type sponse. Raimondi (72) observed a prolonged gastric secretory response 78 per cent of the 96 patients with a "proven roentgen diagnosis of uodenal ulcer" that were studied with the caffeine test-meal. Similar ndings were reported by Musick et al. (73). Why should caffeine cause a olonged stimulation of gastric secretion in the ulcer patient? The most ely explanation we can offer at present lies in the concept of a caffeine d histamine synergism.

Summary

Careful clinical observation indicates that smoking, consumi alcoholic beverages, and coffee drinking may each contribute to delay healing of peptic ulcer or to recurrence of the disease. None of these thr items plays more than a contributory role in the pathogenesis of t disease.

Nicotine. There is no good evidence that tobacco smoking stimula gastric secretion or motility. How smoking exerts its deleterious effect those cases in which symptoms are precipitated or accentuated by smoki is not known. We suggest that studies be made on the effect of smoki on blood flow through the gastric mucosa.

Alcohol. Alcohol is both a gastric irritant and a gastric secreto stimulant. Since both of these actions can aggravate peptic ulceratio there is justification for the interdiction of alcohol in the management ulcer patients.

Caffeine. Caffeine is a moderately potent stimulant of gastric secr tion. It would appear that there is a marked variation in sensitivity of t gastric secretory mechanism of man, cat, and dog to caffeine stimulatio

Caffeine provokes vascular changes in cats which make the muco membrane hyperemic, engorged, and succulent.

Caffeine is capable of producing gastroduodenal ulcers in cats a guinea pigs when the drug is gradually absorbed from a beeswax vehic to permit its continuous action.

The majority of patients with active peptic ulcer respond to t caffeine test-meal by a prolonged and sustained stimulation of the tot output of free hydrochloric acid. This type of response may be due to t synergistic action of caffeine in combination with histamine liberat from the gastrointestinal tract. It would be of interest to determi whether the secretory response reverts to normal with remission symptoms and inactivity of the ulcer process.

We do not mean to leave the impression that caffeine causes ulc in man. However, in view of the prolonged gastric secretory response ulcer patients, caffeine may aggravate an ulcer already existing and m render the therapeutic management of the condition more difficult.

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UTLINE OF CHAPTER 12

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Comment

CHAPTER 12

Role of the Nervous System

Introduction

The possibility that peptic ulcer is largely or entirely neurogenic origin has received the attention of numerous investigators over a peri of more than 100 years. Experimental work in this field was first stimula by the clinical concept that a connection existed between intracran disease and gastric hemorrhage. Just who originated this concept, i difficult to say. Jäger (1), in 1811, took issue with Hunter's explanat of the softening and perforation which Hunter described as occurr postmortem in individuals dying a violent death. Hunter believed t this phenomenon was the result of loss of the "living principle," so t the stomach, after death, could no longer resist the corrosive action gastric juice (see Chapter 4). Jager opposed this view on the basis several instances in his experience where the stomach had been involv before death; and since, in most of these cases, the primary symptoms a pathologic changes were those of an irritative intracranial lesion, Ja suspected that a connection existed between the two conditions.

The association of erosions, hemorrhages, and acute ulcers of stomach and duodenum with the occurrence of intracranial disease been amply confirmed clinically (44).

As early as 1837, the two schools of thought on the subject of gas duodenal lesions in association with intracranial disease were sufficie well crystallized to merit an extensive discussion by Imlach (2), wh paper covers the earlier literature. Rokitansky (3), in 1842, suggested t the gastromalacia and ulceration associated with brain and menin lesions was "perhaps based primarily on disturbed innervation of vagus nerve and overacidification of the gastric juice."

Partly on the basis of these considerations, and partly from the covery of lesions in the stomach incidental to experimental procedure the nervous system, attempts were made to produce ulcers of the up digestive tract by damage to, or stimulation of, the various parts of nervous system. These efforts met with no success, and it was ultima on clinical grounds that Bergmann (31) formulated a "neurog

heory" of peptic ulcer. He envisioned the ulcerative process as beginning ith an erosion produced by spasm of the gastric musculature; continued r repeated spasm prevented the healing of the erosion and caused it to rogress to a chronic ulcer. The motor disturbance in the stomach was egarded by Bergmann as one manifestation of a generally disordered or nbalanced vegetative nervous system in an individual of a "neurotic eneral constitution."

At the time he promulgated his theory and for some years afterwards, ergmann (32) was firm in the conviction that the vegetative imbalance ı ulcer patients embraced the entire autonomic system, not one of its ivisions. In his opinion, the terms "vagotonia" and "sympathicotonia" ere to be discouraged. "I have never thought," he wrote, "and I have ever stated that the development of gastric ulcer is to be considered pendent solely on an increased 'vagotonus.' Everywhere, from the nters, from the preganglionic and postganglionic fibers, from the napses, but mainly from the plexus within the organ and especially the uerbach plexus, arises the disharmony which leads to spasm."

Some reviewers contend that Bergmann must nevertheless have cognized a predominance of parasympathetic phenomena, inasmuch he repeatedly emphasized that hypermotility and hypersecretion were e characteristic "neurotic stigmata" in the stomach. And certainly his sociate, Westphal (33), clearly leaned toward the concept of vagotonia. e that as it may, Cushing's (15) version of a neurogenic theory left no ubt that in his opinion the primary disturbance was to be sought in the rasympathetic component of the autonomic system. He outlined e probable mechanism as follows: from a parasympathetic center the diencephalon, probably in the tuberal cell clusters, fiber tracts ss to the autonomic stations in the midbrain and medulla, the vagal cleus being the most important of these stations. Experimental lesions ywhere in the intracranial course of these fiber tracts from anterior pothalamus to vagal center, presumably from parasympathetic stimula- n (or possibly from vagal release due to sympathetic paralysis), are one to cause gastric erosions, perforations, or ulcers.

The experimental literature which existed before these theories were oposed and that which followed could be interpreted as supporting nost any viewpoint. There are plenty of conflicting observations and nflicting interpretations. In an effort to avoid repetitiousness, and to ep from obscuring the overall picture by belaboring the details, we will cument the reports briefly, and in tabular form wherever possible. Our ief preoccupation in this chapter will be with those investigators who ve advanced the problem by contributing evidence rather than un- pported opinions.

Lesions of the Central Nervous System

In 1846, Schiff (4) described the occurrence of multiple small mucosa hemorrhages in the stomach following damage to the optic thalamus i dogs and rabbits. At that time he attributed the gastric lesions to dilata tion and stasis of the blood vessels resulting from a vasomotor paralys due to destruction of the central vasomotor center. Brown-Sequard (5 disagreed with this interpretation. He described a "wine-red conditio of the gastric mucosa" and a perforated ulcer in a dog with a lesion of th surface of the cerebrum produced by cautery with a hot iron. Accordin to Brown-Sequard, the process in the stomach consisted essentially of contraction of the arteries and veins; the blood is thus driven from bot sides towards the capillaries which, gorged with blood, rupture.

Ebstein (6) produced lesions of the anterior corpora quadrigemina 23 rabbits through trephine openings in the skull. He found ecchymoses the stomachs of nine of these animals during an observation period up seven days. This conscientious investigator did not conclude that pept ulcers result from damage to the corpora quadrigemina; he went on show that similar gastric lesions occurred following injury to the gr matter of the cervical cord, prolonged stimulation of the central end the cut sciatic, injury to the labyrinth or inner ear, or the injection strychnine subcutaneously. Moreover, he observed intestinal hemorrhag also subpleural ecchymoses, in animals with damage to the centr nervous system. One of his dogs developed a deep duodenal ulcer addition to extensive extravasations in the stomach following hemisecti of the cord at the level of the fourth cervical vertebra. In Ebstein's opinic it was unlikely that the gastric hemorrhages resulting from such diver lesions could be explained by a single mechanism.

Similarly, Albertoni (7) noted a high incidence of gastrointestin hemorrhages and erosions following lesions of almost every part of t brain in rabbits, dogs, and pigeons; when quinine sulfate was admin tered to counteract the vasospasm, there was a marked reduction in t frequency of the lesions. Ewald (8), in collaboration with Koch, repor that when the blood pressure was lowered by transection of the cervi or lower spinal cord in six dogs, there occurred numerous lentifo gastric ulcers which appeared punched out and reached the submuc The experiments were up to 36 hours in duration. We (52) obser hemorrhages and erosions in dogs following removal of large portion the cerebral hemispheres.

Hemorrhages and ulcerations in the stomach of the rabbit w reported to follow lesions of the crura cerebelli, corpora quadrigem

ns, floor of the fourth ventricle and ala cinerea (9), and of the cerebral duncles, optic thalamus and Ammon's horns (10, 11).

The experiments reviewed thus far were of the acute or semiacute type, animals surviving from a few hours to a few days at the most. In most tances, the animals were doubtless in a state of shock for all or part of postoperative survival period.

Observation periods of longer duration began with the work of rdenko and Mogilnitzki (12), who pointed out that previous investiga- s had not given ample attention to the influence of vegetative centers en analyzing the mechanism of ulcer production following damage to brain. In experiments carried out by these authors, lesions of various rts of the midbrain in the area of localization of the vegetative centers re made in nine dogs; hemorrhages occurred in a number of organs d tissues, among which was the gastrointestinal tract. In the latter, the ons were said to consist of hemorrhagic erosions, acute ulcers, and atrized and chronic ulcers. While the authors stated definitely that se were not classic "round ulcers" in the clinical sense, they suggested t bilateral damage to the extrapyramidal tracts and vegetative centers ates favorable conditions for the development of ulcer. It is interesting t chronic ulcers were described as being present in the stomachs of two heir dogs as long as 74 days and one year after operation but no gross microscopic pictures of these significant lesions accompanied their per. No ulceration appeared in control experiments in 19 dogs with ons of the temporal lobes, Ammon's horns, or the pons.

Battaglia (13) autopsied 31 dogs in which various parts of the brain re damaged; two large duodenal ulcers were said to have been found a dog with lesions of the optic thalamus. During studies on the relation the central gray nuclei to pulmonary circulation, Oberling and Kallo) noted gastric lesions in six dogs and six rabbits but none in cats and nea pigs; the lesions appeared from 20 hours to 15 days after damage he central gray nuclei, and consisted of diffuse congestion, hemorrhagic sions, and ulcers involving chiefly the pylorus. Histologic studies indi- ed that the lesions resulted from vascular stasis, hemorrhage, and estion of the infarcted mucosa.

Light et al. (16), in confirmation of some experiments of Cushing (15), orted the occurrence of a high percentage of acute ulcerations in the machs of rabbits within three hours after the injection of large doses pilocarpine into the lateral ventricles. They believed that the lesions e due to stimulation of vegetative centers adjacent to the third and rth ventricles, with passage of the impulses through the autonomic vous system to the viscera. According to Ferguson (17), however, more

than 100 intraventricular injections of pilocarpine in massive doses fail to cause any gastric or intestinal lesions in 15 monkeys.

Watts and Fulton (18), who found occasional superficial ulceratio of the stomach in monkeys from a few days to nine months after placi hypothalamic lesions, believe that the gastrointestinal effects are d primarily to a release or irritation of the sympathetics. Hoff and Sheeh (19) reported gastric erosions occurring within a few days in five of monkeys in which the hypothalamus was damaged, but it seemed to the improbable that lesions of the hypothalamus so small as those made their experiments could stimulate the sympathetic pathways or destr enough of these pathways to produce a parasympathetic predominan Large doses of mecholyl (25 to 50 mg. per kilo), or of adrenalin (0.5 1:1000), or of the latter combined with atropine (1.5 cc. adrenalin p atropine 20 mg. per kilo) injected into monkeys every two or three ho for three to seven days did not result in gastric lesions.

Ulcer-like erosions of the gastric mucosa of cats following localiz lesions of the frontal cortex were reported by Mettler et al. (20). Ko (21) produced increased intracranial pressure in rabbits by placing sponge in the third ventricle and reported superficial lesions of the stoma in seven of 22 animals during a period of from three to 273 days. In f dogs sacrificed from 48 hours to 30 days after damage to the optic tha mus, and in four dogs examined during similar intervals after lesions the hypothalamic region, Chiariello (22) found vascular types of lesi in the antral and pyloroduodenal mucosa. This was confirmed for b rabbits and dogs by Matsukuma (23), who claimed further (24) that incidence of gastric lesions following damage to the midbrain was marke reduced by simultaneous bilateral subdiaphragmatic vagotomy, but by celiacectomy.

Keller (25) has made the most extensive report on ulcerations in digestive tract following intracranial procedures and has published ex lent gross and microscopic figures illustrating his findings. However, numerous observations are difficult to interpret, perhaps because studies were not primarily planned to identify the cranial centers tracts concerned in the production of digestive tract lesions. Keller interested primarily in studying the heat-regulating mechanism, and brain lesions were placed accordingly. Digestive tract lesions consist of hemorrhages and craters in the stomach and duodenum were obser only in those animals in which damage was produced in the brain st However, it was Keller's impression that an alteration in the cerebrosp fluid by contamination with blood and debris from the lesions played s part in the gastrointestinal disturbance. Since both hemorrhagic a and craters occurred in the same locations, and since the craters w

bserved in those animals which lived longer after operation, the author first considered the hemorrhagic areas to be the precursors of the aters. He was led to qualify this view as a result of later experience, in hich he observed (1) that the two types of lesions were not seen in the me stomach simultaneously, and (2) that, whereas the hemorrhages ccurred after complete destruction of the anterior portion of the hypo- alamus, craters were never encountered unless a part of the anterior ypothalamus was intact.

We know of only one report describing the results of a planned study this problem, using precision methods. Martin and Schnedorf (26), perimenting in 40 cats and seven monkeys, produced accurate lesions the hypothalamus with a minimum of trauma to other brain structures. side from four cats dying within a week after operation, the animals ere sacrificed at intervals from 20 to 190 days postoperatively. All of the imals remained in good nutritional condition; no bloody stools or mitus were noted at any time; studies of gastric motility and secretions five monkeys and three cats (no data are given) showed no significant fference due to the hypothalamic lesion; and in none of these animals as there any evidence of abnormality in the gastrointestinal mucous embrane at autopsy.

Comment. It has been demonstrated beyond doubt that hemorrhages, osions, and acute ulcers of the stomach and duodenum occur in associa- n with intracranial damage or disease. It has *not* been shown that these ute digestive tract lesions depend on a disturbance in the diencephalon, uch less in some particular center within that division of the brain (75). nd no acceptable evidence has yet been presented to show that a *chronic* ptic ulcer results from experimental lesions of the brain. As Keller (25) ted: "It should be stressed that no sign of a non-healing defect was ever countered that simulated chronic clinical gastric and duodenal ulcers." eller suggested the possibility that the mucosal changes might become ronic in the presence of recurring hemorrhages or tumors; however, the ts are against this possibility. *In 1932, Cushing (15) could find only one case his series in which a chronic ulcer was associated with a brain lesion;* if we con- er that Cushing's experience by that time embraced well over 1000 ses, we are impressed, not with the possible frequency of the association, t with its rarity. It may be argued that no special attention had been rected towards the search for ulcers in these cases; however, Davis (27), o has been watching for ulcer and ulcer-type dyspepsias in his brain nor patients, has not yet observed such association in a series of some 0 cases. In a series of 512 patients with tumors of the pituitary gland served at the Mayo Clinic, only five (1 per cent) had an associated ptic ulcer (99).

Evidence of ulceration is thus even less frequent in individuals wi intracranial tumors than in the population at large. It is only *after* oper tion on these tumors that ulceration occurs, suggesting that it is not t destruction but rather the irritation of brain tissue that leads to digesti tract ulcerations which, moreover, are always acute. Perhaps if an ind vidual were to survive a long time with a low-grade irritative lesion the brain or meninges, these acute gastroduodenal lesions might becon chronic. This might conceivably be the basis of the "tabetic ulcer," f example, although this would be difficult to prove. Vonderahe (28), in study of the histopathology of the brain in 14 cases of human peptic ulc observed focal hemorrhages in the dorsal motor nucleus of the vagus a in the thalamic and hypothalamic areas. However, similar lesions we found in association with other diseases, and Vonderahe was of the opini that the brain lesions might be the result of abnormal afferent impul from diseased areas of the digestive tract or peritoneum. Cushing (15), proposing that peptic ulcer results from a disturbance in a diencepha vegetative center, referred to irritative disturbances, but apparently d not have in mind a structural alteration of these centers. He mention two possible sources of disturbance; one, a diffusion of the secretion the posterior pituitary into the hypothalamic region and/or into t cavity of the third ventricle and, second, cortical or psychic influence. either case, the theory was that excessive parasympathetic activ resulted, which led to the production of ulcers. "Thus," Cushing wr "it is possible to reconcile the neurogenic theory of ulcerations sponso by Rokitansky and Virchow's modified theory of a primary local cau whether the lesions are considered in terms of simple erosions, of ac perforations, of autodigestive softening, or of chronic ulcers, and whet they chiefly involve esophagus, stomach, or duodenum."

Since the only proven part of this concept is that erosions, acute p forations, and "autodigestive softening" occur in association with int cranial procedures, this is the only aspect of the theory which me examination at the present time. The question is, what is the nature these digestive tract lesions and what is the mechanism of their prod tion? In other words, what is the histophysiology of the ulcerative chan

In the first place, the basic lesion is not specific to the "ulcer arc Burdenko and Mogilnitzki (12), in summarizing their experiments, m it clear that disturbances of the interbrain resulted in hemorrhage various organs and tissues, "among others also in the mucosa of gastrointestinal canal." Ebstein (6) made a similar observation s 50 years earlier. Keller (25) describes ulcerations of the mouth in following lesions of the brain stem, and it appeared that these ul developed and healed *pari passu* with those in the stomach. These b

ers started as a hyperemia, progressing to focal hemorrhages which veloped into penetrating ulcers; here we have a hemorrhagic process olving a mucous surface and going on to ulceration without the sence of acid pepsin.

All observers, from Schiff (4) onwards, have described focal hemorges into the gastric mucosa following brain damage. The description en by Light et al. (16) is particularly good and we will quote it:

> The earliest change is found at the surface of the mucosa and consists of a number ny hemorrhages from adjacent capillaries. . . . The change of color which accomies the breakdown of the erythrocytes is an indication of the depth to which the l chyme has penetrated into the tissue. In these small superficial hemorrhages the r change extends only a few cells deep. The mucosa beneath such lesions is usually ceably anemic, with collapsed capillaries. Necrosis and slough of the superficial layers marks the next stage . . . in a few instances there are engorged vessels in mucosa of the affected area and in the muscularis mucosae. As a rule, however, tissue is anemic in the region of the necrosis, in contrast with the partly filled llaries of the unaffected tissue on either side. With further extension of the process, osis occurs to the level of the muscularis mucosae, but rarely deeper. Of leucocytic mphocytic reaction there seems to be none, because of the short duration of the ess and the sluggish circulation present. Areas of focal necrosis are found frequently e longitudinal and circular muscle bundles of the stomach.

In the experience of other observers, the focal hemorrhages were ially more extensive, involving almost the entire thickness of the cous membrane.

Another type of acute lesion, namely, ischemic necrosis progressing to on-hemorrhagic erosion, has been described by Burdenko and Mogilski (12) and by Keller (25), and these observers associate this lesion the function of a circumscribed portion of the hypothalamic area.

Much discussion has revolved around the question of the genesis of e lesions; investigators have sought to find in the character of the on a clue to whether it resulted from spasm of the gastrointestinal culature or from purely vasomotor phenomena, and, if the latter, ther the change was essentially one of vasoconstriction or vasodilata-, and whether the predominating disturbance lay in an impairment e parasympathetics with excessive sympathetic activity, or vice versa, so on. We have shown in Chapter 8 that either a hemorrhagic erosion n ischemic erosion may result from a disturbance of a number of the hanisms concerned in preserving the integrity of the mucosal cells, consequently it is futile to attempt to identify one particular mecha- without direct evidence. Keller (29) thought that the location of e lesions on the crests of the folds in the secretory area of the stomach ested that the primary disturbance lay in the secretory process. If by he implies an excessive action of acid, his own observations, as well

as ours, are against it. He obtained mucosal hemorrhages in the absenc of free acid, and in our experience, when acid is dripped on the mucosa focal hemorrhage does not occur until after the surface epithelium ha sloughed off, exposing the hyperemic vessels.

Certainly one does not have to postulate excessive vagal activity t account for the mucosal hemorrhages; on the contrary, Keller's worl indicates that after bilateral vagotomy the placing of a lesion in the brai stem is followed by focal hemorrhages in the stomach, identical in a respects with those observed following brain-stem lesions with the vag intact. The importance of this contribution is that, while it does no eliminate the possibility that the vagi *may* be concerned in the genesis mucosal hemorrhages from central irritative impulses, it shows that th parasympathetic pathway *need* not be concerned. Then, if Keller's wor can be confirmed, there could be no doubt that *interruption of the vag route still leaves open a pathway over which abnormal or excessive impulses fro the vegetative centers in the brain can exert a deleterious effect on the upper digesti tract.*

Keller (29) reported further that, in contrast with the mucosal hemo rhages discussed above, the development of the ischemic lesion, whic quickly passes over into an erosion, seems to depend on the integrity the vagus. When prechiasmal damage was produced without vagotom mucosal craters (erosions) appeared as the characteristic lesion; but, bilateral vagotomy was performed first, these erosions did not develo In discussing the mechanism of this phenomenon, Keller examines, a rejects, the likelihood of a primary vasoconstriction as explaining t ischemic erosion, and we are inclined to agree. We cannot go along wi his suggestion that a derangement of the gastric secretory process is t primary factor. Keller did not take into account the possible role of co traction of the muscularis mucosae, which seems to us an importa possibility. Further discussion of this point must be postponed until t experiments on vagus stimulation and interruption are reviewed later this chapter.

Boles and Riggs (30), on the basis of autopsy studies, concluded th there was no essential pathologic difference between the acute lesio associated with primary intracerebral disease and those found in t absence of such disease. These authors propose an interesting conce which we quote:

> While the intracranial lesion is the immediate factor initiating cerebral vegeta activity, the stimulating effects of resulting peripheral circulatory disturbances on vegetative system itself may establish a vicious cycle. Normally peripheral vaso striction due to central vegetative control insures adequate cerebral blood sup however, excessive stimulation of this physiologic mechanism may result in anoxi

ics and later in increased capillary permeability, tissue edema and decreased ulating blood volume. Tissue edema thus established augments the irritability of cerebral centers through the mechanism of asphyxia and, because of its demyelinizeffects on peripheral nerve pathways, may render the entire vegetative system itive to subminimal stimuli. In turn, the vasoconstriction of vessels resulting from ormal neural irritability aggravates the preexisting stasis.

The experimental evidence does not support this view because, in mals surviving intracranial lesions, the acute ulcerations heal.

A factor which must be kept in mind in evaluating the digestive tract ons associated with intracranial operations is the degree of shock proed by the procedure. The relation of the state of shock to acute lesions he digestive tract has been discussed in Chapter 8.

Procedures Involving the Autonomic Nerves and Ganglia

According to Imlach (2), the following experiment was reported by nerer and Autenreith (51): "On cutting the nerves of the stomach, it, the *par vagum* of each side, and the splanchnic branches of the great pathetic in a living animal, the lesion (erosion of the stomach) was ced in the living but paralyzed organ by the natural gastric juice." ach (2), in 1837, was unable to reproduce these lesions "in a few mpts at" cervical vagotomy in cats and rabbits. After a lapse of about arter of a century, experimentation on the relation of the autonomic m was gradually resumed. In the interest of logical presentation, it nvenient to deal first with disturbances of the parasympathetics, then e sympathetics, and finally with combined lesions of the two divisions.

Parasympathetic Disturbances

Stimulation of the Vagus

n 1890, Talma (94) reported that stimulation of the left vagus nerve wo to six hours in rabbits caused marked spasm and acute superficial ration of the pyloric region. This is readily confirmed in the dog when n occurs. Keppich (63), in 1921, prepared an electrode which was duced into the abdominal cavity in rabbits, encircled both vagi, and brought out through the posterior abdominal wall. Of 11 rabbits cted to prolonged electrical stimulation of the vagi by this method, 10 doped gastric lesions; five of these were described as chronic ulcers. technique of Stahnke (92) consisted of placing an olive-tipped tube e esophagus just above the cardia and stimulating the vagi by insertan electrode into the tube. The author attempted to simulate a nic irritation of the nerves by stimulating for 20 minutes twice daily; esulted in the production of superficial gastric erosions in two dogs.

When the stimulation was carried out daily for 96 days, hypermotility hypersecretion, and interference with gastric emptying were produced On the basis of such experiments, the author believed that the origin of ulcers through nervously influenced hypersecretion must be accepted Best and Orator (48) produced chronic irritation of the vagus by wrapping a strip of magnesium around the right or left nerve in six dogs; no ulcers were observed after a period of from one to six months.

Ettinger et al. (34) stimulated the cervical vagus electrically in anesthetized dogs several hours daily for as long as 200 days. Only congestion of the mucosa of the stomach and duodenum was noted at autopsy Manning et al. (35) carried out continuous electrical stimulation of the cervical vagus in unanesthetized dogs for from 70 to 90 hours. Only one animal, which received eserine in addition to the vagal stimulation, showed antral and duodenal ulcerations.

Production of Parasympathetic Overactivity by Pharmacologic Methods

Westphal (33) was able to produce hemorrhages and erosions of the stomach in rabbits, cats, dogs, and guinea pigs by injection of enormous doses of pilocarpine. In one rabbit, it was observed at laparotomy that the stomach exhibited strong peristalsis and cyanosis when the pilocarpine was injected; the animal was sacrificed after one hour, and erosions of the mucous membrane were present. That HCl was necessary for the formation of these lesions was demonstrated by the fact that no erosions occurred in a pilocarpine-treated animal when the stomach was perfused with sodium chloride solution. The author concluded that the basis of the genesis and chronicity of peptic ulcer is a purposeless increase in the neuromuscular function on the stomach. Westphal's findings were confirmed by Nicolaysen (80), who considered the hemorrhagic lesions a result of circulatory disturbance produced by contraction of the muscular ture of the stomach. Haeller (101) denied that the ulcerative lesions could be produced by pilocarpine injections on the basis of spasm, but his work was criticised and refuted by Hayashi (102) and Nakashima (103). The latter injected macacus monkeys with 0.75 to 2 cc. of adrenalin and 3 to 4 cc. of 1 per cent pilocarpine daily for three months; at the end of the period there were no lesions in three of the monkeys, erosions in one deep erosions in one, and a large perforating ulcer in another. The experiments led the author to conclude that the spasmogenic theory logically accounts for the occurrence of peptic ulcer. Production of ulceration in the stomach of rabbits by subcutaneous injection of large doses (10 to 30 mg. per kilo) of pilocarpine was also reported by Underhill and Freiheit (104), but since they could not duplicate these results in cats and rats, they considered the phenomenon a species peculiarity. Friedman

05) used doses of 25 to 50 mg. of pilocarpine in rabbits and noted acute sions in every case. Hanke (120–122) produced acute erosive gastritis administering very large doses of pilocarpine, acetylcholine, or insulin.

Five hundred cubic centimeters of 1:10,000 acetylcholine was administered by intravenous infusion daily for 26 to 235 days to eight dogs Hall et al. (36). Congestion and minute erosions of the gastroduodenal ucous membrane were the only findings at autopsy. Wener and coorkers (112) observed erosions, hemorrhages and, in a few instances, stric and duodenal ulcers in dogs receiving large daily doses of mecholyl ther in aqueous solution or suspended in beeswax.

We (83) administered pilocarpine every two hours for 37 days to 13 gs and obtained nothing more than mucosal hemorrhages. More cently, we (113) administered the parasympathomimetic drug Urecholine in beeswax to dogs in doses ranging from 2 to 33 mg. daily for from to 51 days. Hyperemia and a few erosions were the only lesions found.

Comment. No one has satisfactorily shown that chronic peptic ulcer ay be produced by prolonged stimulation of the vagi or by the proged administration of parasympathomimetic drugs. This is not to say at peptic ulcer *may not* be produced by such methods if a better technique worked out for maintaining a simulated "vagotonia" continuously. r instance, when we gave 2 mg. of histamine every two hours day and ght for two months, we thought we were obtaining a continuous action the drug, but we did not produce ulcers. Yet, when histamine is given beeswax in a total daily dose only slightly greater than that used in our periments, ulcers develop in considerably less than two months. owever, it is very difficult to sustain a high gastric secretory level by the eated administration of a parasympathomimetic drug, because all of se drugs produce a reversal of effect, that is, inhibition rather than nulation, as the dose is increased or as the cumulative action of a small, repeated dose sets in (114). Accordingly, the lesions which do occur en large doses of these drugs are given appear to arise primarily on a cular basis. Furthermore, they are not confined to the stomach but ur throughout the alimentary tract and even in other organs.

In 1920 in two dogs we anastomosed the central end of the phrenic ve to the peripheral end of the vagus just above the diaphragm. When ified after several months, no ulcers were found but evidence of siologic connections of the phrenic with the gastric plexus could not demonstrated. This experiment should be repeated, but the fact that ring the cut vagus does not lead to restoration of function indicates t the vagus is incapable of regeneration and may account for the re of the cross-suture experiment.

The primary lesion following the production of simulated vagotonia

is a mucosal hemorrhage. Westphal (33), Nicolaysen (80), and other attributed the lesion to contraction of the musculature of the stomach especially the muscularis mucosae. The erosion which follows was a tributed to the action of acid on the area of focal hemorrhage. Apparently this is as far as Bergmann's hypothetical "vicious cycle" goes in th experimental animal, because the erosions, instead of progressing t ulcers, heal while new hemorrhages form.

Vagotomy

In Rabbits. The literature contains reports both affirming (21, 45–4 60, 62, 67, 80, 82, 87, 95, 98) and denying (55, 57, 59, 71, 72, 74, 96, 9 the occurrence of gastric lesions following vagotomy in rabbits. Much the data is clearly valueless because of the short observation periods, th small number of animals, and the failure to classify the lesions accuratel A summary of the more reliable data (Table 16) on this phase of th

Table 16

Gastric Ulcer in Rabbits Following Bilateral Vagotomy

Observers	*Date*	*Number of Animals*	*Observation Period*	*Ulcers*
Van Yzeren (95)	1901	20	8–289 da.	10
Donati (55)	1904	11	16 hr.–120 da.	0
Ophüls (82)	1906	30	3–88 da.	6
Zironi (98)	1908	38	3–107 da.	19
Kawamura (62)	1911	10	1–92 da.	0
Antonini (46)	1914	20	1 da.–5 mo.	2
Beazell (47)	1936	29	7–117 da.	12
Koga (21)	1937	18	2–31 da.	3

problem shows that the incidence of true ulcer is considerable. V Yzeren (95), the first to make a careful study of the occurrence of ulc in rabbits following vagotomy, observed that the incidence of ulc increased *pari passu* with the survival time of the animals. The lesions h the following characteristics: (1) located in the pyloric region at or ne the lesser curvature; (2) usually single; (3) no tendency to heal; (4) pr ceded by necrosis of the mucosa; (5) no involvement of the surroundi tissue; (6) the gastric secretion was not materially different from norm during the time of development of the ulcers. The author also fou that the ulcers were usually prevented from appearing for a period from 20 to 50 days by section of the musculature along the pylorus or an efficient gastroenterostomy. Van Yzeren's explanation for the develo ment of ulcers following vagotomy is noteworthy; he suggested that

ere is an increased irritability of the gastric ganglion cells, rendering e stomach very susceptible to reflex excitation, and (2) there may be a ophic influence of the vagi on the mucosal cells and on the blood vessels.

Donati (55) felt certain that gastric lesions could not be produced by tting the nerves supplying the stomach; however, there is evidence that failed to cut all of the vagal fibers. For instance, he observed no dilata- on of the stomach within the first two to four weeks after operation. roni (98) reported an incidence of 50 per cent, while Antonini (46), spite his efforts to assure complete vagotomy by performing the opera- on transthoracially, obtained ulcers in only two of his 20 rabbits. We (47) und that the incidence of ulcer in vagotomized rabbits increased as the rvival period increased; the maximum incidence of 65 per cent was ached in about 50 days.

Crescimone and Anglesio (53) reported that bilateral vagotomy in- nsified the ulcerations which develop following the injection of hemo- ic agents. Finocchiaro (57) could not confirm this.

In Dogs. Concerning the development of ulcer in dogs following inter- ption of the vagi, the literature is less contradictory. The results have ually been reported as negative (47, 54, 55, 61, 62, 70, 77, 86), occasion- y as doubtful or unconvincingly positive (29, 37, 46, 60, 74, 116). It was ted by Brisotto (50) that ulcer resulted from the administration of drochloric acid to dogs with bilateral cervical vagotomy. Meek (78) orted the occurrence of two cases of gastric ulcer in 13 vagotomized gs in which gastric stasis was intensified by feeding dry dog biscuit.

Galli and Polacco (58) denervated the stomach by sectioning all ible nerves on both surfaces (Latarjet method) in 10 dogs; in 17 other gs, this was supplemented by circular incision of the muscularis just oximal to the antrum. In addition, the arterial supply to the lesser vature was ligated in some of the animals. The reported incidence of er in dogs surviving these procedures at least 30 days was 25 per cent. riche et al. (68) did not obtain ulcers in three dogs observed for two nths after the Latarjet denervation; however, in a dog in which a eral gastrojejunostomy was performed simultaneously, an ulcer was orted to have developed, but the authors neglected to mention where. s doubtful whether a complete vagal denervation was achieved by the thod employed in these experiments.

In Other Animals. In monkeys, bilateral vagotomy (cervical in five, diaphragmatic in three) was reported by Ferguson (17); in this series, re was one case of perforated duodenal ulcer and one of gastric erosion. guinea pigs observed from 10 hours to 15 days after vagotomy did not elop ulcers (46). Komarov (115) observed rats which had been vagot- ized for periods as long as 4 months and he reported no ulcers. Midulla

(79) showed that vagotomy in frogs and toads leads to the developme of multiple gastric erosions, which may go on to ulceration and eve perforation.

Mechanism of Ulcer Following Vagotomy. The rabbit is the onl laboratory animal in which there is no doubt that ulcers develop cor sistently after the vagus nerves are cut. The location of these ulcers significant; in our experience they always appear along the lesser curva ture in the pyloric antrum near the incisura. Owing to technical diffi culties, the effect of vagotomy on gastric secretion in the rabbit has n been studied. Ophüls (82) found the postmortem acidity of the gastr contents of the animals in his series to be normal both in the rabbits wi ulcer and in those without. Certainly one would expect that, if vagoton affects the acidity in rabbits, it probably does not raise it, so it is unlike that the ulcers are due to excessive acid.

The most obvious gross disturbance of gastric function followi vagotomy in rabbits is in the motility. Distention of the stomach to twi its normal capacity is not unusual. In our experience, this distention is longer present after the fiftieth postoperative day, which is significant view of our further observation that, if an ulcer is destined to develop ir vagotomized rabbit, it will appear within 50 days. Consequently, we co sider stasis to be the chief predisposing factor. We obtained eviden that a rough diet is also a factor, inasmuch as the incidence of ulcer w reduced by approximately 50 per cent when the animals were placed a soft diet postoperatively. The only two clear-cut instances of ul following vagotomy in dogs (78) occurred in the presence of stasis and rough diet.

Nicolaysen (80) made an observation which is of considerable inter and, if it can be confirmed, of importance. He reported that artific ulcers of the anterior wall of the stomach healed in vagotomized rabb while spontaneous ulcers were developing on the lesser curvature. T phenomenon made it difficult for Nicolaysen to account for the pe vagotomy ulcer; if rough food, or loss of trophic influence, were fact in the development of the spontaneous ulcers, why did they not a prevent healing of an ulcer already present? The only suggestion we offer is that the lesser curvature has anatomic and functional peculiari which make possible the development of ulcers in the rabbit just as man. Thus Yano (97) reported that vagotomy definitely delayed healing of artificial ulcers on the lesser curvature.

Lichtenbelt (37) insisted that gastric ulcer develops in dogs, just a rabbits, after the vagi are out. But neither his protocols nor his ot studies lend credence to this conclusion. For example, in studying effect of vagotomy on secretion, he stated that he obtained a psyc

retion of gastric juice from an autotransplanted pouch of the stomach. It is difficult to determine from the literature how the postvagotomy er starts. Keller (29) mentions the presence of edema of the mucosa in gs, and Midulla (79) describes the same thing in frogs. This would rhaps be compatible with a loss of trophic function. More study of the ject is required, and now that vagotomy is being used as a treatment peptic ulcer, the opportunity for careful gastroscopic observation of e gastric mucosa from the immediate postoperative period onward will ubtless not be overlooked.

On the basis of our experimental observations and the evidence avail-le in the literature, we (38) called attention to the possibility of gastric er developing in humans if vagus resection is practiced widely. To te, we have heard of the occurrence of four such instances.

Disturbance of Sympathetic Supply to the Stomach

In many of our physiologic studies, we performed splanchnicectomy d lumbar sympathectomy on dogs which have subsequently been served for as long as several years. In only one instance have we served an ulcer of the stomach in such a dog (11).

Pincus (40) is cited by several authors as having been the first in-tigator who removed the celiac ganglion in a large series of experiments. of his animals died within 30 hours; autopsy revealed hyperemia, norrhage, and ulceration of the gastroduodenal mucosa in many cases, ecially in dogs. Popielski (39) removed both celiac ganglia and the erior mesenteric ganglion from 22 dogs. All developed bloody diar-a. Complete autopsy protocols were given for only five of the animals l all of these were described as having ulcers in either the stomach or odenum. Prevertebral ganglionectomy, consisting of removal of both iac ganglia and the superior and inferior mesenteric ganglia, was per-med on nine dogs by Lium (41). All developed bloody diarrhea, and tic ulcers were found in four of the dogs at autopsy. Lium attributed discrepancies in the results of various workers to the variation in the ensiveness of ganglionectomy and he proposed the ulcers might be due part to the inanition caused by the diarrhea.

Both of these opinions were upheld by the recent studies of Lillehei l his co-workers (117). These investigators, in order to insure the npleteness of denervation, in addition to extirpating the ganglia also pped the nerve plexuses from around the blood vessels for a distance 7 to 8 cm. from the aorta. They found that when this procedure was formed on the celiac and the superior and inferior mesenteric ganglia, ere bloody diarrhea occurred. In addition, ulcers of the stomach and odenum occurred in about 50 per cent of the dogs. Besides the gastro-

duodenal ulcers, occasionally an ulcer would occur as far down as t terminal ileum or colon. In six animals in which only the celiac a superior mesenteric ganglia were removed, three died in from 11 to days with severe diarrhea and gastroduodenal erosions and ulcers. T three surviving dogs were found to be unusually sensitive to histamine beeswax administration, all succumbing with perforated ulcers with five days. In 12 dogs, only the celiac ganglion was removed and in the animals no vomiting or diarrhea ensued. However, when these anim were given histamine in beeswax for five days three to 500 days after t denervation operation, all showed severe gastroduodenal ulcerati Among 21 intact dogs receiving histamine in beeswax alone for just 5 d ulcers occurred in only 2. Unfortunately, none of the animals in wh only celiac ganglionectomy was done were sacrificed without receiv histamine. However, the fact that none of the animals in which only t celiac ganglion was removed succumbed spontaneously from perforat or hemorrhage indicates that the severe diarrhea which accompan removal of the superior and inferior mesenteric ganglia contributes to ulceration of the stomach and duodenum when the celiac ganglia removed simultaneously.

It is clear that postganglionic sympathetic denervation has much m severe effects than preganglionic denervation.

Of the many other workers who have investigated this question, o Dalla Vedova (54), Alvarez (45), Koennecke (64), and Durante contended that by interfering with the sympathetic fibers to the stom it was possible to produce ulcers resembling those found in humans. remaining reports are summarized in Table 17; none of the aut included in this list noted anything more than focal lesions, either f irritation or from excision of sympathetic nerves.

Visscher (118) stimulated the splanchnic nerves continuously three weeks in dogs and observed a hypertension during this pe Evidence of peptic ulcer was not observed.

Comment. Elimination of the sympathetic supply to the stomach been performed experimentally on the assumption that it should prov method for the production of autonomic imbalance such as is pres to be present in some peptic ulcer patients. The evidence is contradi because the extent of denervation has varied considerably, and the e of pre- and postganglionic denervation differ. There are a numb clinical observations on sympathectomized patients.

Barron (107–109) made a long series of balloon kymograph stud two juvenile diabetic patients who had had a two stage splanchnicec Shortly after left splanchnicectomy, short periods of intense motility were noticed, interrupted by short periods of quiescence

Table 17

EFFECT OF IMPAIRMENT OF SYMPATHETIC INNERVATION OF THE STOMACH

Observers	*Date*	*Animals*	*Procedure*	*Observation Period*
an (43)	1863	dogs	Extirpation of celiac plexus	3–30 da.
ansky (65)	1866	rabbits, cats, dogs	" " " "	7 hr.–8 wk.
uel (89)	1886	rabbits, cats, dogs	" " " "	1 hr.–3 da.
ig* (73)	1889	rabbits, dogs	" " " "	7–73 da.
er* (84)	1890	rabbits	" " " "	3 wk.–4 mo.
i* (81)	1891	dogs	" " " "	1½–2 mo.
in (69)	1894	rabbits	" " " "	1–200 da.
rassini* (76)	1903	rabbits	" " " "	..
ati* (55)	1904	rabbits, dogs	" " " "	3 da.–4 mo.
pfer (91)	1906	dogs	Bilateral section of 4th to 9th dorsal roots	1 da.–4 mo.
(71)	1909	rabbits	Extirpation of celiac plexus	10 hr.–14 da.
nincke (90)	1910	..	Stimulation " " "	..
amura (62)	1911	rabbits, dogs	Extirpation " " "	1–166 da.
i* (70)	1912	dogs	" " " "	50 da.
nte (56)	1913	rabbits, dogs	Left splanchnicotomy	5 hr.–46 da.
cati (49)	1914	dogs	Right lumbar sympathectomy	1 da.–4 mo.
delfinger (61)	1918	dogs	Stimulation of celiac plexus and extirpation of celiac plexus	To 30 da.
in (93)	1920	dogs	Extirpation of celiac plexus	wk.–mo.
y (85)	1934	rabbits, guinea pigs	Perisplanchnic injection of toxins	hrs.
e also ref. 66)				
r* (29)	1936	dogs	Bilateral removal of sympathetic chain	1–14 da.
(21)	1937	rabbits	Bilateral splanchnicotomy	1–47 da.

These authors reported no changes in the gastroduodenal mucosa; all others ted lesions varying from hyperemia to acute ulcerations.

ods of activity soon become longer and, occasionally, would last ughout a four to five hour period of observation, or more typically, e would be a period of motility which ended in gastric tetany. After ort period of quiescence, the motility would resume and continue ughout the period of observation. After right splanchnicectomy, the ts were similar. There was continued prolonged intense gastric lity and this lasted without change for the seven months that one

patient was followed. Gastric emptying time was studied in one of th patients and, while no significant decrease was noted after right unilate splanchnicectomy, the average total emptying time decreased from f hours 45 minutes to three hours 30 minutes following the bilateral splan nicectomy. Barron (110) concludes that splanchnicectomy removes t inhibitory component of the autonomic nervous supply to the stoma Much more evidence must be accumulated before these points will established. More studies like those done by Barron, and done on hyp tensives, for example, are necessary. His two patients, it must be reme bered, underwent splanchnicectomy for the treatment of diabetes, a though their insulin requirement was found to decrease postoperative they still required insulin. Barron states that the blood sugar level v well controlled by careful therapy with insulin and dextrose. But no d on this is given, and the fact that occasional "hypoglycemia periods" w observed and quickly corrected in his patients indicates the need of d which will avoid this possible complication.

Mason (42) studied an ulcer patient who had undergone splanch cectomy for hypertension 18 months previously. In balloon kymogra tracings made on five different occasions, the degree of quiescence v the most characteristic feature. The periods of activity, which usu lasted 20–40 minutes, consisted of tonus rhythm and Type I contracti As a rule, these periods occurred only once during a 3–4 hour study, a appeared while the patient was asleep, but somewhat more freque when the patient was awake. A drop in the pH of the gastric juice below 2.0 or 3.0 usually accompanied this activity.

Mason (42) recently reviewed the literature on peptic ulcer follow splanchnicectomy and presented detailed protocols of 10 cases recor at the University of Michigan Hospital. He could not obtain satisfact evidence that the occurrence of peptic ulcer following splanchnicecto was a result of removal of the sympathetic innervation. The fact that ulcer or a history of ulcer was present before operation leaves open possibility that the ulcer might have recurred regardless of the surg Patients with the longest history consistently developed the more ser complications; those with recently healed ulcers and especially pati with active ulcers developed complications most rapidly after splanc cectomy, and these complications were usually the most severe that w present in this group of patients. It was Mason's impression that w splanchnicectomy does not predispose to ulcer, it favors the develop of complications in ulcer patients because the change in the type of experienced deprives the patient of the warning that the ulcer is recurr Two cases of a painless perforation of a peptic ulcer in such patients h been observed (119).

Interruption of All Extrinsic Nerves to the Stomach

This has been successful in only a limited number of animals because ne seriousness of the procedure; section of the vagi and removal of the ac plexus, with the occasional removal of one or more additional ominal sympathetic plexuses, has been reported in a single animal by ral authors; the data are summarized in Table 18.

Table 18

Interruption of Vagus and Sympathetic Fibers to the Stomach

Observers	*Date*	*Animals*	*Observation Time*	*Ulcers*
Adrian (43)	1863	1 dog	12 da.	0
Samelson (88)	1879	1 dog	30 da.	0
Donati (55)	1904	1 dog	30 da.	0
Lilla (71)	1909	2 rabbits	25 & 40 da.	0
Gibelli (106)	1909	4 dogs	7–53 da.	0
Kawamura (62)	1911	1 rabbit	41 da.	0
Ivy (100)	1920	10 dogs	1 wk.–4 mo.	0
Alvarez (45)	1929	19 rabbits	2–27 da.	3
Keller (29)	1936	3 dogs	36 da.–3 mo.	0
Koga (21)	1937	18 rabbits	1–8 da.	4

n our experience (11, 100), dogs dying immediately after section of agi and splanchnics not infrequently show petechial hemorrhages e pyloric and duodenal mucous membrane. But in 10 dogs that died re killed from one week to four months following bilateral vagotomy splanchnicotomy with extirpation of the celiac plexus, no gastric or enal lesions were found. In our studies on the nervous pathways ved in enterogastric regurgitation (111), we observed a large number imals with vagotomy, splanchnicotomy, and celiac ganglionectomy ately or in combination and no gastroduodenal lesions were found topsy.

Comment

this chapter, we have reviewed those procedures involving the us system designed to produce in various animals the picture of n peptic ulcer. These experiments have involved damage to almost part of the brain, stimulation or section of one or both vagus nerves ious points in their accessible course, section or manipulation of the hnic nerves or of the abdominal sympathetic plexuses, or complete sic denervation of the stomach. None of these procedures, with the tion of bilateral vagotomy in rabbits, has consistently given rise to

chronic gastric ulcer; gastric ulcer occurs much less frequently in th vagotomized dog. It is significant that the acute lesions which are pro duced in the stomach by interference with the nervous mechanism almo always begin as a focal hemorrhage or ischemia. Here, then, is one fie where it is generally agreed that the vascular, rather than the acid facto initiates the mucosal injury. Theories as to the genesis of the acute lesio are: (1) Vasomotor changes, (2) spasm of the muscularis or muscula mucosae, and (3) trophic changes. But the histophysiology of these lesio has been confused by the fact that the primary lesion appears to be t same whatever part of the nervous system is damaged and regardless whether the disturbance consists of irritation or interruption.

In view of clinical observations, the most logical experimental approa to the neurogenic theory of peptic ulcer is not to separate the stoma from its nervous connections but to devise an effective method of send a constant stream of impulses over these nerves. Clinically, such a d turbance is presumed to be present in a chronic state in the "anxi complex," and in a relatively acute state following operations on cert parts of the brain. Experimentally, establishment of the chronic st has been attempted without success. Perhaps the acute state has b duplicated by damage to the brain in animals, but the reports are sufficiently consistent to permit any conclusions. The latter approach the problem will be susceptible to systematic investigation when neurophysiology of the visceral centers is better understood.

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TLINE OF CHAPTER 13

Intestinal and Urinary Extracts

NTEROGASTRONE

A. PHYSIOLOGY

B. PREPARATION OF AN ENTEROGASTRONE CONCENTRATE

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ROGASTRONE

A. PROPERTIES OF UROGASTRONE

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UMMARY

CHAPTER 13

Intestinal and Urinary Extracts

The concept that hormones of the digestive tract may be concerned in the problem of peptic ulcer is relatively recent and research in this field is still in the formative stages. A careful documentation of the chronological sequence of reports and utterances relating to the discovery of anti-ulcer substances has been prepared by Sandweiss (1).

Enterogastrone

Physiology

The inhibitory effect of ingested fat on gastric secretion was reported by Ewald and Boas (2) in 1886 and was subsequently confirmed and studied in further detail by a number of investigators.

The existence of a humoral agent for gastric motor inhibition by fat was proved when we (3) were able to demonstrate that the introduction of fat into the main stomach of a dog inhibited the motility of a subcutaneously autotransplanted pouch of the stomach. Feng et al. (4) employed the same technique to show that the inhibition of gastric secretion by fat also involves a humoral mechanism. Kosaka and Lim (5) described the preparation from the small intestine of an extract capable of inhibiting gastric secretion; they named the active principle "enterogastrone," from the Greek enteron (intestine), gastron (stomach), and chalone (inhibition). We (6) obtained more potent enterogastrone concentrates and defined the unit of this substance as that amount which, when injected intravenously in a 12 to 14 kg. dog with a pouch of the entire stomach receiving sufficient histamine subcutaneously at 10 minute intervals to maintain a uniform flow of 1 cc. of gastric juice (approximately 5 mg. HCl) per minute, causes a 50 per cent reduction in the secretion of hydrochloric acid during the two hours following the injection.

Preparation of an Enterogastrone Concentrate

Lim et al. (5) prepared enterogastrone from the small and large bowel of dogs, first by hydrochloric acid or saline, and later (7) by picric acid

extraction. We obtain the material in large quantities from the intestinal mucosa of hogs; at present we are using the following method:

The source material employed is the first six to eight feet of small intestine from freshly slaughtered hogs. It is extremely important to get the intestines as soon after slaughter as possible. Intestines more than 30 minutes old are likely to give a poor yield of enterogastrone and to give a product with high vasodilatin content. The strips of intestine are everted at the abattoir, washed with water, and suspended in cold 0.4 per cent HCl with occasional stirring, in the proportion of 80 liters to 400 intestinal strips. At the end of 30 minutes, the intestines are removed and wrung out by hand into the acid extract, which is then strained through cheese cloth and shaken vigorously with sufficient dry NaCl to saturate it, or about 30 per cent of the weight of the acid extract. The resulting suspension is brought back to the laboratory and the precipitate is collected by filtration to the consistency of a stiff paste, which has a total solid content of about 35 to 40 per cent. This product, designated "A-precipitate," has, in our experience, served as a highly satisfactory source of all the gastrointestinal hormones. Uniformly potent enterogastrone concentrates are obtainable from this product stored under refrigeration for up to two to three months. About eight kilos are obtainable from 400 intestinal strips.

Purification is effected by suspending three kilos of A-precipitate in 30 liters of water with the aid of a Waring blender, adjusting the suspension to its isoelectric point, pH 5.4, by the addition of NaOH solution, bringing the adjusted mixture to a boil with a current of live steam, and filtering off the precipitated and coagulated inert material. The clear filtrate is cooled with running water and treated with a saturated solution of pure (resin-free) tannic acid to the point of complete precipitation, in the proportion of about 100 cc. to 4 liters of chilled filtrate, and the resulting precipitate centrifuged out, washed by suspension with distilled water, 5 per cent acetic acid, and finally with water. It is then triturated thoroughly with 70 per cent aqueous acetone containing 2 per cent of its volume of concentrated HCl, the suspension centrifuged vigorously, and the supernatant fluid filtered into eight to 10 volumes of pure dry acetone. The insoluble, inert residue is washed with acidified acetone and the washings are combined with the first extract. Throughout the manipulation of the tannic acid precipitate, the temperature must be low and the centrifugings brief in order to avoid a gummy product which is difficult to handle, and the entire process must be continuous without pause.

The abundant colorless amorphous precipitate resulting from the flooding of the acid-acetone extract with acetone is allowed to settle, the supernatant fluid siphoned off and discarded, and the precipitate centrifuged out and washed twice with absolute methanol containing 1 per cent of its volume of concentrated HCl, and finally with acetone. The acetone-wet precipitate is dissolved in a large volume of cold distilled water; for the yield from 3 kilos of A-precipitate (amounting to about 60 grams in dry weight), 15 liters of water is used. To this solution is added a saturated solution of picric acid in warm acetone to the point of complete precipitation; the above-mentioned amount requires approximately 150 grams of picric acid. The resulting precipitate is centrifuged out, packed tightly in the cups, and then is triturated with the same acid-acetone mixture employed to decompose the tannate, using a Waring blender to consummate a thorough mixing. The resulting suspension is centrifuged long and hard, the supernatant fluid decanted into an excess of acetone, and the residue washed with acid acetone and the washings added to the first extract. The residue is discarded. The white amorphous material precipitated by the acetone treatment is centrifuged out, washed repeatedly with acetone until all traces of picric acid are removed, then with

a 1:1 mixture of acetone and dry ether and finally ether, and is dried in vacuo. Ap proximately 30 grams are obtained from 3 kilos of A-precipitate. The product is colo less, easily soluble in water, and possesses an average unitage of 25 milligrams repressing histamine-induced gastric secretion in the total pouch dog. It has little, any, inhibitory action on gastric motility, in contradistinction to the cruder produ prior to the picric acid treatment. Tests on a series of guinea pigs have revealed it to b entirely nonantigenic.

For purposes of injection, the material is dissolved in boiling sterile water in a co centration of 50 milligrams per cc. and stored in sterile rubber-capped bottles. O casional tests have revealed such solutions to remain sterile and potent up to 10 da after bottling; periods of storage of longer duration have not been tested.

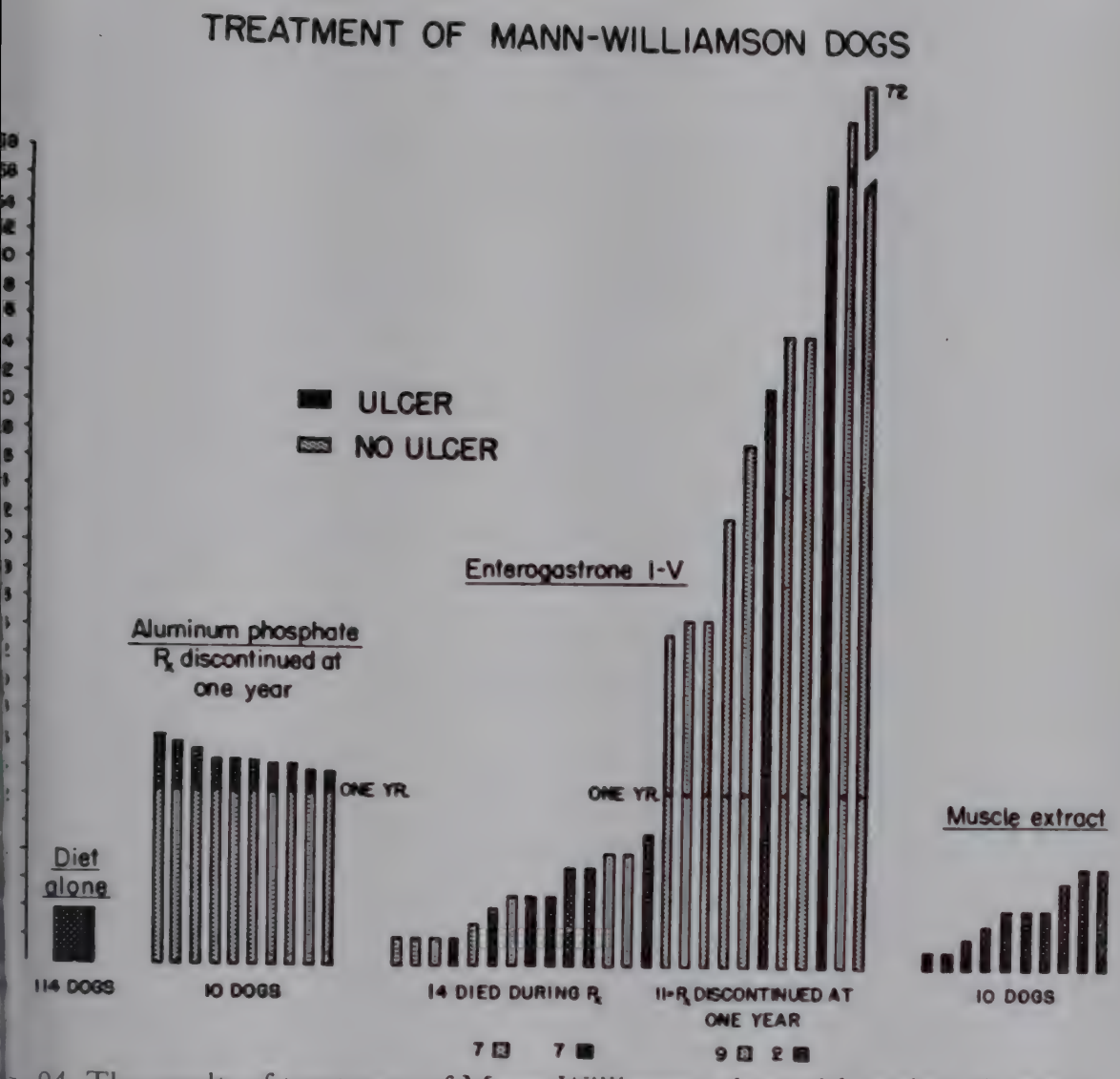
Use of the Enterogastrone Preparation to Prevent Ulcer in Mann-Williamson Dogs

In our first experiments on the effect of enterogastrone in Mann-W liamson dogs, we (8) administered the preparation intravenously in mg. doses three times daily with the thought that this might inhibit secr tion sufficiently to prevent postoperative jejunal ulcer. It turned out th although the gastric secretion was not significantly affected in these a mals, jejunal ulcers failed to develop in 75 per cent of dogs. Moreov enterogastrone appeared to have conferred on these animals a considera "immunity" against ulceration.

Of the 25 dogs in this series, six died with ulcer within one ye Eight dogs died within nine months from various other causes with ulcer. The 11 dogs which survived one year were explored surgically a found to be free from ulcer. After preventing ulcer for one year in th eleven dogs, treatment was discontinued and the dogs observed for development of ulcer. Nine of the 11 dogs died from causes other th ulcer in from 11 to 60 months after cessation of the treatment. Two of 11 dogs died with ulcer 18 and 28 months after cessation of treatm

The incidence of ulcer in this group of animals during the first y was 24 per cent. This figure is to be compared with an incidence of per cent in a series of 114 untreated M-W dogs (see Fig. 94). A special c trol series of 10 dogs, treated with an extract of pork muscle prepared the same process used in making the enterogastrone concentrates, all d with ulcer in an average of 16 weeks. This finding established the imp tant fact that the beneficial effect of intestinal extracts is not due to s nonspecific substances extractable from all tissues.

That the "immunity" to ulcer produced by treatment with ent gastrone concentrates for one year is prolonged is indicated by the c cited. It is, however, not always permanent; two animals died with u 18 and 28 months after cessation of treatment. The fact that some of t animals do, in time, develop ulcer constitutes evidence that the resist



g. 94. The results of treatment of Mann-Williamson dogs with various therapies. uminum phosphate prevented the ulcers as long as its administration was con-ued, but when it was stopped all the animals developed ulcers. When treatment th enterogastrone was stopped, a prolonged "immunity" to ulcer formation was ted.

ulcer formation is due to the enterogastrone therapy rather than to some t of adaptation to the operation.

In subsequent studies, we (9) demonstrated that subcutaneous ad-nistration of enterogastrone concentrates once daily for periods as short three months either immediately preceding or immediately following M-W operation provides definite protection against the occurrence of er and "immunity" or resistance to ulcer formation after cessation of atment. *The significance of these observations is to be judged in the light of the t that when ulcer is prevented in Mann-Williamson dogs by feeding aluminum sphate or mucin, the withdrawal of these agents is followed by the development of nal ulcers within four months.*

It is to be noted that we pursued the investigation of enterogastrone h the expectation that it should be useful in the treatment of peptic

ulcer by inhibiting gastric secretion, and perhaps motility. We [illegible] obtained evidence that in Mann-Williamson dogs treated with enterogastrone, the gastric secretory curve in response to alcohol is not as profound as in the untreated dogs. However, the chronic daily subcutaneous administration of enterogastrone concentrates to normal dogs or to gastric pouch dogs in amounts effective against M-W ulcers did not depress the gastric secretory capacity as measured by hydrochloric acid or pepsin secretion in response to histamine and alcohol (12). It was concluded that while treatment with enterogastrone extracts did not decrease the ability of the gastric glands to respond to a given stimulus, it did eliminate an abnormal type of gastric stimulation present in untreated M-W dogs [see p. 3[illegible]].

The use of enterogastrone in human peptic ulcer patients will be discussed in Chapter 22.

Urogastrone

Properties of Urogastrone

The prophylactic value of preparations of anterior-pituitary-like hormone (extracts of pregnancy urine) in M-W dogs was at first considered possibly to be due to an inhibitory effect of this hormone on gastric secretion (Chapter 317). However, subsequent studies have shown (1) that although urine extracts containing A.P.L. hormone depress gastric secretion in gastric pouch dogs when administered in relatively large doses subcutaneously (11), such extracts are effective against ulcer formation in M-W dogs in doses too small to inhibit gastric secretion when given by the subcutaneous route (12); (2) that extracts of nonpregnant female urine (13) as well as male urine (14, 15) contain a substance which depresses gastric secretion; and (3) that extracts of urine from nonpregnant females as well as from males (16) are effective in preventing M-W ulcers. Thus it has been shown (1) that the inhibitory effect on gastric secretion of extracts containing A.P.L. hormone is due (at least in part) to some substance other than the contained A.P.L. hormone and is a property of extracts from both sexes; and (2) that the ulcer-preventive factor in these extracts is also independent of its content of A.P.L. hormone, being present in the urine of males and nonpregnant females.

The nature and properties of the gastric secretory depressant [illegible] have been the subject of numerous investigations. It has been differentiated by Gray and associates (34) from a number of other substances which are known to occur in urine, including sex hormones (17), the pressor [illegible] of the posterior lobe of the pituitary (18, 19), kallikrein (17), and [illegible] (20, 21). Because it appears to be a distinct entity, and until its relation to enterogastrone can be established, the name urogastrone has been [illegible]

ray and co-workers (20) for the gastric secretory depressant in urine. rogastrone has been shown to be effective in depressing histamine-lated gastric secretion in man (22, 23, 36), dog (14, 17, 24), cat, a pig, and pigeon (24). Friedman and co-workers have reported that strone is present in the urine of patients with duodenal or gastric (13), as well as in those with gastric cancer or pernicious anemia (25). ic motility is also inhibited by urogastrone (14, 17, 24, 26), but the required is higher than that necessary to inhibit secretion and the is short-lived. Curiously, urogastrone (and enterogastrone) do not t gastric motility in the vagotomized stomach pouch of the dog (27). tempts have been made to determine the site of origin of urogastrone e factors which control its excretion. Although preliminary experi- by Culmer and co-workers (28) indicated that enterectomy abol- and the feeding of fat enhanced, urogastrone secretion, thereby sug- a relationship to enterogastrone, subsequent more extensive studies y and collaborators (29, 30) failed to provide complete confirmation er of these claims.

was concluded from these latter studies that the apparent excretion gastrone is decreased by removal of the small intestine and increased ingestion of a high or low fat diet. With the evidence at present le, no definite conclusions can be reached as to whether or not trone represents an excretory product of enterogastrone. A final de- on this important question must await the application of improved ls assuring quantitative recovery and isolation of urogastrone from cific substances.

ulbersz (41) has found that the output of urogastrone is decreased ophysectomy. Gastrectomy and duodenectomy do not depress uro- e excretion, according to Friedman and associates (31). In a series e experiments on dogs, Friedman (32) and Friedman and Sand- 24) found that the gastric secretory inhibitory effect of urogastrone pressed by enterectomy. Schiffrin and Gray (33) reinvestigated this n in semichronic enterectomized gastric pouch dogs and found rone to be fully effective in inhibiting secretion. The possibility that r-preventive factor in urine extracts might be due to prolactin was ated by Friedman and Podolsky (35). They found that urine ex- otent in preventing M-W ulcers have no prolactin activity.

Anti-ulcer Effect of Urogastrone

he same constituent of urine extracts responsible for depression of secretion and prevention of M-W ulcers? Sandweiss and co-workers that these activities are due to two separate principles. This con- is based on the following observations: (1) Extracts of urine of

normal male and female persons as well as peptic ulcer patients inhibit gastric secretion (24) and gastric motility (26) when administered in small doses (1 to 5 mg.) intravenously, whereas only urine extracts from normal males and females protect against M-W ulcers, the extracts from the urine of ulcer patients being ineffective (37). (2) The small subcutaneous doses of urine extract used in the treatment of M-W ulcers are incapable of inhibiting gastric secretion in normal or M-W dogs, in single or repeated daily doses (38). (These small doses are, however, effective when administered intravenously; the ratio of the subcutaneous to intravenous minimum effective dose is at least 5 to 1.) This indicates that the mechanism whereby urine extracts prevent M-W ulcers is not, at least entirely, the inhibition of gastric secretion. (3) A high percentage of the ulcers which develop in M-W dogs being treated with urine extract show a tendency toward healing, whereas a healing ulcer is a rare finding in untreated animals (37). From these observations, Sandweiss et al. conclude that the beneficial effect of urine extracts in the treatment of M-W ulcers is not due to the gastric secretory depressant, urogastrone, but to some other factor which promotes healing (fibroblastic proliferation and epithelization).

The evidence upon which this conclusion is based must be regarded as incomplete. In Table 19 appear the results obtained by Sandweiss and his co-workers in the treatment of M-W ulcers with various types of urine extracts (compiled from several papers by these authors). In the last column to the right, the percentage of dogs in each group which were benefited by treatment is indicated. These workers considered a dog benefited by treatment if (1) it died without ulcer, or (2) it survived longer than 135 days (the maximum survival time in the control group), or (3) it died with ulcer but the ulcer showed evidence of healing. The last criterion must be considered arbitrary and has not been employed by other workers in this field. Nevertheless, by their own criteria, the difference in the percentage of animals benefited by urine extracts from ulcer patients and by normal male urine extracts (24 per cent and 37 per cent respectively) is not statistically significant. The most striking difference is between female (pregnant and nonpregnant) urine extracts and male (ulcer and non-ulcer) urine extracts (average of 74 per cent and 31 per cent benefited, respectively).

Although present evidence indicates that the mechanism of the beneficial effect of urine extracts is not a depression of gastric secretion, the possibility still remains that the same substance which inhibits secretion exerts some other action which is responsible for the prophylactic value of the extracts in M-W ulcers.

This view is supported by the fact that the preparations of both uro-

Table 19

RESULTS OF TREATMENT OF M-W DOGS WITH URINE EXTRACTS*

Type of Treatment	*No. of Dogs*	*Died with Ulcer*		*Average Postop. Life (Days)*	*No. of Dogs Living More Than 135 Days*	*No. of Ulcers Showing Evidence of Healing*	*Per Cent Dying of Perforation*	*Per Cent of Dogs in Group Benefited by Treatment‡*
		No.	*Per Cent*					
Control No Treatment	28	28	100	71	0	2	72	7
Extract of Pregnancy Urine	42	23	55	206	12	9	20	85
Extract of Urine from Normal Females	42	34	74	172	15	10	54	62
Extract of Urine from Normal Males	38	34	89	259	12	2	64	37
Extract of Urine from Ulcer Patients	30	27	90	71†	3	2	76	24

* Compiled from the data of D. J. Sandweiss and co-workers.

† Four dogs in this group were sacrificed at 70 days postoperatively.

‡ Dogs were considered to have benefited from treatment if a) there was microscopic evidence of healing when the dog died with ulcer, or b) the dog died without ulcer, or c) the dog lived longer than the maximum length of life of control dogs (135 days).

gastrone and enterogastrone have this dual activity, i.e. anti-ulcer activity and antisecretory activity. Furthermore, there is some evidence that urogastrone (gastric secretory depressant) excretion in ulcer patients is less than in normal individuals (30, 40), and this may be correlated with the tendency of the urine from ulcer patients to be less effective in combating the M-W ulcer. Until either the anti-ulcer factor or the gastric secretory depressant have been isolated chemically, judgment must be reserved on whether or not they are separate entities.

In regard to the stimulation of healing by urine or intestinal extracts, it cannot yet be determined whether this is due to direct action of the

substances on the intestinal mucosa or to the withdrawal of some influenc which promotes ulcer formation. It would be of interest to determine th effect of urine extracts on the rate of healing of defects produced by surgic excision in isolated jejunal loops.

Perhaps the most promising aspect of the effect of urinary and intest nal extracts on M-W ulcers is the failure of ulcer to occur in these anima when the injections have been discontinued. Sandweiss (39) has reporte that six M-W dogs treated with urine extracts by daily injection for or year or longer failed to develop ulcer 11 months after therapy was witl drawn, thus paralleling the action of intestinal extracts.

Recently a great deal of attention has been given to the use of intestin and urinary extracts in the prevention of the ulcerations which occur the rumen of rats with ligated pylorus (see p. 273) (42) (43). Risley (44) h concluded from his studies that the prevention of ulcers by these extracts brought about by inhibition of acid secretion. Before the significance these studies on rumenal ulcers in rats can be fully evaluated, we shall ha to learn more about the comparative effectiveness of anti-ulcer and an secretory substances in the rat, dog, and man.

Similarity of Urinary and Intestinal Extracts

It will be noted that a remarkable similarity exists between "u gastrone" and "enterogastrone." In each case, an extract of biolo material is capable of inhibiting histamine-stimulated gastric secret when injected intravenously in small doses (or considerably larger dc subcutaneously). Furthermore, both are effective against M-W ulcers subcutaneous doses too small to cause significant depression of gas secretion. Finally, both possess the notable property of conferring upon animal resistance to the formation of ulcer for long periods after tl administration has been discontinued. Sandweiss believes that neither term enterogastrone nor urogastrone should be employed in referrin the principle in intestinal or urinary extracts which protects against ul in M-W dogs. He points out that enterogastrone is, by definition, chalone which inhibits gastric secretion and motility, and it was upon property that its application to the treatment of peptic ulcer was ba Since, however, the anti-ulcer effect is manifested without any effec gastric secretion and motility, he believes it is probable that the ac anti-ulcer principle of the intestinal extracts, as well as of the urine extr is a separate and distinct entity. To designate this principle he propose term anthelone (*anti*—against, *helcos*—ulcer). Regardless of whether anti-ulcer and antisecretory factors are the same or different compon of these extracts, the mechanism whereby they produce their anti-u effect remains unexplained.

Summary

A substance can be extracted from the intestinal mucosa (enterogas-one) and another from the urine (urogastrone) which inhibit gastric cretion when they are given intravenously in small doses. These same xtracts delay or prevent the appearance of ulcers in a high percentage of Iann-Williamson dogs, even when given in doses too small to depress cretion. Whether the anti-ulcer and antisecretory action are due to the me component of these extracts cannot be decided until one of these ctors has been isolated. The mechanism of the anti-ulcer effect is not iown.

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OUTLINE OF CHAPTER 14

Postmortem Incidence in Relation to Pathogenesis

I. Introduction
II. Basis of Selection of Data from Autopsy Reports
III. Analysis of the Autopsy Data
    A. incidence of peptic ulcer
        1. Chronologic Changes
        2. Geographic Differences
        3. Racial Differences
    B. incidence of gastric ulcer
        1. Chronologic Changes
        2. Geographic Differences
        3. Racial Differences
        4. Changes in Sex Incidence
        5. Age Incidence
    C. incidence of duodenal ulcer
        1. Chronologic Changes
        2. Geographic Differences
        3. Racial Differences
        4. Sex Incidence
        5. Age Incidence
    D. ratio of gastric to duodenal lesions
IV. Summary of the Present Status of Our Knowledge Concerning the Autopsy Incidence of Peptic Ulcer
    A. ulcer of the stomach
    B. ulcer of the duodenum
    C. ratio of gastric to duodenal ulcer
V. Discussion
    A. incidence of peptic ulcer
        1. Geographic and Racial Differences
        2. Age Incidence
            a. Sex Hormones
            b. Gastric Secretion
            c. Dietary Excesses
            d. Psychosomatic Factors
            e. Infection

B. ULCER OF THE STOMACH
   1. Absence of a Recognizable Trend in the Incidence of Gastric Ulcer
   2. Change in the Sex Ratio of Gastric Ulcer
      a. Emotional Tension
      b. Chlorosis
      c. Tight Lacing

C. DUODENAL ULCER
   1. Increasing Incidence
      a. Greater Consumption of Alcohol, Tobacco, and Caffeine-containing Beverages
      b. Psychogenic Factors
   2. Predominance of Duodenal Ulcer in the Male Sex
      a. Anatomic Differences in the Upper Digestive Tract
      b. Gastric Secretion
      c. Sex Hormones
      d. Psychosomatic Differences

I. CONCLUSION

CHAPTER 14

Postmortem Incidence in Relation to Pathogenesis

Introduction

It is important to study variations in the incidence of peptic ulcer f possible clues to the factors concerned in the etiology of the disease. T three sources of information on the incidence of any disease are: (1) clinic statistics, which indicate how frequently the disease is diagnosed in relati to the number of hospital admissions or patient visits within a given peri of time; (2) mortality rates, which indicate how many people die of t disease in relation to the living population within a given period; and (autopsy figures, which indicate how frequently the disease is observed in consecutive series of individuals dying from all causes. In addition, in t case of peptic ulcer, as in other diseases where a clinical diagnosis may made by x-ray examination in the absence of symptoms, we must recogni as a fourth source of information the x-ray incidence.

Deductions based on a changing incidence as derived from clini statistics are contestable principally because the alleged changes may only a reflection of improvements in diagnostic methods. Nor is t apparent change necessarily in the direction of an increase; for instan in reference to the sex incidence of gastric ulcer, Habershon (40) stat

> It is sufficiently obvious that in hospital or private practice women suffer m often than men from some of the symptoms of gastric ulcer; but it is probable, tha the actual state of facts could be proven many of these would have to be regrouped cases of gastralgia, subacute gastritis, or gastric catarrh.

Generally, however, the more accurate the recognition of a dise entity, the higher is its clinical incidence. An interesting example is fou in the comments by Roberts (95) on peptic ulcer in Uganda: "the nat of Uganda has sheltered gastric and duodenal ulcer from view under cloak of *kifuba* (pain in the chest). Attention was drawn to this subj by the admission of a case of perforated duodenal ulcer in June 1 Since then fourteen cases of *kifuba* have undergone surgical treatment gastric and duodenal ulcer, a clear and typical history being obtained the exercise of patience."

The value of mass x-ray surveys (145, 176) of the upper digestive tract an indication of the incidence of peptic ulcer is at present limited cause of the difficulties of visualizing many ulcer craters, particularly the duodenum, and because of uncertainty whether duodenal deformity reliably indicative of existing or pre-existing ulcer.

Mortality rates cannot provide an index of the frequency of a disease less it is known how many of the people who have that disease die from The latter figure could only be obtained from autopsy reports on the al and nonfatal incidence of the disease in a large series of deaths from causes. The fact is that, on the basis of mortality statistics (51), gastric er might seem much more frequent than duodenal ulcer, whereas nically the relationship is reversed and at autopsy the diseases are ghly equal. This simply means that the ulcer is more lethal when ated in the stomach.

We agree with Brinton (10) that "nothing short of a large number of ropsies can afford any valid basis for our conclusions as to the fre- ncy of the disease (gastric ulcer)"; but *autopsy reports, too, can be grossly leading, as we are about to see.*

Data on the incidence of peptic ulcer in necropsy material have been quently quoted, and their significance speculated upon, with little or concern for their statistical validity. Thus, Gruber (36) stated: "In the nerous works on the incidence of gastric ulcers, few authors have en the trouble to read the previous statistics in the original. As a result, . errors have crept in . . . ." Yet Gruber's own compilation of vious statistics is by no means a critical one, and it even contains gross rs.

It is obviously futile to speculate on the etiologic implications of the ying incidence of peptic ulcer without examining the validity of evidence for such variations. We have, therefore, reviewed, from inal sources as far as possible, a considerable number* of reports on incidence of peptic ulcer at necropsy.

* The review is not exhaustive because: (1) We have not included the Russian ature on this subject. However, Hamperl (41) states (a) that in dealing with the ian autopsy reports one is never certain whether the incidence cited includes the atal cases, and (b) that there are only three surveys in which the sex ratio of peptic was calculated properly. (2) We have not located any reports from France, Spain, aly, although it is likely that data from these countries are on record somewhere. nstance, Rodman (97) mentions the findings of Professor Donati at the University urin (2.6 per cent gastric ulcers in 8000 autopsies), but gives no bibliographic nce. We have not yet traced this report. However, this is not to be construed as ying that autopsy data is, as Portis (89) remarks, "difficult to gather." There is no ulty whatsoever in gathering it—the problem is to evaluate the data which is able.

Basis of Selection of Data from Autopsy Reports

In an attempt to limit the tabulations to autopsy data that is, or ca be rendered, comparable to some degree, we have adhered to the followi plan:

A. A report was deemed inadmissable for the purposes of our princip tabulations when:

a. The autopsy series consisted of less than 1000 cases: Dahlerup (16 Jones (55); Muller (75); Wrany (137); Starcke (117); v. Korczynski a Jaworski (59); Holzweissig (47).

b. The autopsy material was not representative of the population large: Grunfeld (39); Sommerfeld (114); Clark (14); Robertson a Hargis (96); Pollak and Kreplick (87).

c. Erosions or specific lesions, such as tuberculous and maligna ulcers, were included: Stachelhausen (116); Nauwerck (79); Krug (6 Francine (29); Rössle (100).

d. The authors, themselves, pointed out shortcomings which inva dated their figures: Greiss (35); Danziger (17); Oberndorfer (81); Grub (36).

e. The data were not clear as presented: Steiner (119); Wollma (134); Harsløf (43); Schönberg (109); Dietrich (20); Gruber and Kra eisen (38).

f. Data were lacking on both the age and sex composition of t autopsy material: Chambers (13), Lebert (64), Oppenheimer (83), Pe and Shaw (86), Gluzinski (31), Rosenbach (99), Goldschmid (32, 3 Madelung (69); or there was no definition of the lesions to indic whether erosions were included: Stawell (118); or both, i.e., neither a sex data nor criteria for classification of peptic ulcer: Ziemssen (14 Danziger (17), Fenwick and Fenwick (28), Hopf (48), Brooks (1 Howard (49), Rutimeyer (101), Raw (92), White (129), Yukawa (13 Lindner (68), Paus (84), Polya (88), Schrijver (110), Hjort (46), Gord and Manning (34).

However, many of the above authors will be referred to in the disc sions, whenever pertinent.

B. A number of the reports stated that only "adults" were includ in the survey; the "adults" varied from individuals over 10 to those o 20 years. In order to make available as many reports as possible comparison, we recalculated the data from surveys embracing all groups to include only individuals over 10 years old. This is indica in the "Remarks" column of the tables as RTAO 10 (Recalculated adults over 10).

C. In those reports where the sex, but not the age, composition of

opsy population was shown, we have accepted the data as a basis for culating the sex ratio of the incidence. This has been done on the umption that the age distributions for both sexes were comparable, even ugh 50 per cent of the series may have been children and the data refore neither acceptable for total incidence nor correctable to individuals over 10 years. In the following tables, data calculated on this basis indicated in the "Remarks" column as "CAPU" (Composition of opsy population unknown).

D. When erosions were reported separately, or when the lesions were ned in a manner that made it possible to determine how many of the es designated as ulcers were in reality erosions, or when detailed tocols made the distinction obvious, the data were recalculated to ain the incidence exclusive of erosions.

Analysis of the Autopsy Data

Incidence of Peptic Ulcer

Chronologic Changes. When the data on the autopsy incidence of roduodenal peptic lesions are tabulated (Table 20), it becomes evident there have been marked variations in the frequency of this disease in the period for which reports are available; but whether this is a nologic or a geographic phenomenon cannot be ascertained in view ne paucity of reports from a given source in successive years.

For instance, we have not found any data from Prague in the present ury to compare with the figures reported from that city up to 1871. In enhagen, the incidence of open ulcers for the years 1907–1936 (42) ed to be the same as for the period 1907–1910 (104); the earlier study ed a greater frequency of healed lesions. Thus, the disease had arently not been increasing in Denmark up to 1936. In fact, if the very available figure of 13 per cent gastric ulcers and scars in Copenhagen psy material (Dahlerup, 1841) (16) means anything at all, there seems progressively less peptic ulcer in that city as time goes on. A study ne necropsy material in Copenhagen (42), embracing three recent des, is of interest: 1907–16, 7 per cent; 1917–26, 5.7 per cent; 1927–36, per cent.

here was no significant difference between the Berlin figures for –1920 (76) and those for 1913–1916 (44); whereas in Munich peptic was reportedly more than three times as frequent during the years –1912 (37) as for the period 1895–1899 (108). However, perhaps in er of these cities was the time interval between surveys sufficiently to provide a reliable index of any trend in the incidence.

Table 20

VARIATIONS IN THE TOTAL INCIDENCE OF PEPTIC ULCERS AND SCARS AND OF ULCE
ALONE IN ADULT AUTOPSY MATERIAL

Observer	*Period*	*Place*	*Total Incidence Per Cent*	*Open Lesions Per Cent*	*Remarks*
Dittrich	1844–46	Prague	8.5	2.9	RTAO 10
Willigk	1850–55	Prague	4.3	0.8	RTAO 10
Eppinger	1868–71	Prague	7.2	1.6	RTAO 10
Greiss	1873–78	Kiel		3.4	Adults over 1
Schneider	1895–99	Munich	2.0	1.5	Adults over 1
Scheel	1907–10	Copenhagen	9.3	3.7	Adults over 2
Kossinsky	1895–10	Erlangen	4.9	2.7	RTAO 10
Gruber	1899–12	Munich	7.3	5.5	Adults over 1
Hart	1913–16	Berlin	11.8	4.7	Adults over 1
Musa	1919–20	Berlin	13.3	4.3	Adults over 1
Lehmann	1925	Vienna	20.2	3.6	74% Adults o 50
Ophüls	1900–23	San Francisco	2.5	2.3	Adults over 1
Sturtevant & Shapiro	1904–22	New York	2.5	1.8	RTAO 10
Jaffe	1929–34	Chicago	4.6	3.4	RTAO 10 corrected chronic ul
Wright-Smith	1927–36	Melbourne	5.6	5.3	Adults over 1
Hansen	1907–36	Copenhagen	6.1	3.6	Adults over

RTAO—Recalculated to Adults Over.

The figures for the incidence of open ulcers are not nearly so diverg as are those for total peptic lesions, and this raises again the ques whether the autopsy data might be better employed for purpose comparison if scars were omitted.

GEOGRAPHIC DIFFERENCES. Although many extensive autopsy sur have been made in various parts of the world, the data are still not enti adequate to permit a satisfactory separation of geographic differences f chronologic changes or other factors.

Kossinsky's (60) survey at Erlangen showed (Table 20) 4.9 per total peptic lesions, 2.7 per cent open ulcers; Gruber (37) found 7.3 cent and 5.5 per cent respectively in his Munich study covering appr mately the same period. Thus it appears that peptic lesions were 50 cent more frequent and open ulcers twice as frequent at Munich. Bu has been noted previously, Kossinsky's figures for the annual incid revealed marked fluctuations from year to year; and, in the years 1

00, 1905, and 1910, the occurrence of peptic lesions in autopsy material Erlangen equalled or exceeded the average incidence at Munich for years 1899–1912.

In two widely separated cities of the United States, San Francisco (82) d New York (122), the disease was reported with the same frequency 5 per cent).

The incidence, particularly of open lesions, appeared somewhat ater in Melbourne (138) than in Chicago (52) for a corresponding iod of years, but it is questionable to what extent the autopsy material s in each instance representative of the population at large. For mple, Gibbs' (30) Chicago survey included the postmortem records m private as well as charitable hospitals, so that it provided perhaps a ter cross section of the population than did Jaffe's (1935) material from Cook County Hospital. Gibbs' figures, when corrected to exclude sions, yield an incidence (circa 2.5 per cent) approximately half that ained by Jaffe.

But, on the whole, it appears from Table 20 that peptic ulcer has been ed less frequently at autopsy in the United States than in England, on Continent, or in Australia.

Muller (73) considers that if Argentina be an index of the prevalence peptic ulcer in South America, the disease cannot be common on that tinent. He bases this opinion on Pavlovsky's (85) report of Ruiz' data n Rosario, showing 30 cases in 1041 autopsies, or an incidence of per cent; and this figure, moreover, apparently does not include scars. us, the lesion is not significantly less frequent, at least on the basis of this meager autopsy survey, than in North America. Muller (73) states her: "In the Marien Magdalen Hospital, St. Petersburg, with a yearly nission of 3500, not a single case of peptic ulcer was seen. The figures for the year 1910 and may have changed in the meantime."

The fact is that Sommerfeld (114) reported 2.9 per cent peptic ulcers, parently counting only open lesions, at the German Alexander Hospital Men at St. Petersburg. His survey comprised 1920 autopsies performed ing the years 1891–1911. Even allowing for the fact that this hospital ted an exceptionally high number of digestive diseases, we see that e must have been plenty of people with peptic ulcers in St. Petersburg he time when the disease was not being seen at the Magdalen Hospital. for the rest of Russia, the figures of Dawydowsky (18) are instructive. In scow during the years 1923–1927, there were performed 37,899 opsies; gastroduodenal ulcer was recorded as the *cause of death* in per cent. Considering that only 56 per cent of the individuals autopsied e over 15 years of age, the adult incidence of *fatal* peptic ulcer was in

the neighborhood of 1.5 per cent, which leads us to infer that the incidence of the disease is not appreciably different in Moscow than in other large cities of Europe.

Rutimeyer (101) sought to explain on ethnologic grounds the greater incidence of peptic ulcer in northern than in southern Germany, but Oberndorfer (81) obtained autopsy data to show that ulcer was not significantly less common in Munich, a southern city, than in Kiel, a northern one.

The conflicting reports and opinions on this subject led Rössle (100) to remark "that the number of observed cases depends more on the observer than on the geographical area." *

Racial Differences. The most significant and remarkable data showing a racial difference in the incidence of peptic ulcer are those of Kouwenaar (61, 143), Socharto (see Bonne et al. (7)), and Eagle and

Table 21

Geographic and Racial Distribution of Peptic Ulcer Autopsy Data

Observer	*Place*	*Group*	*Incidence*[1] *Per Cent*
Kouwenaar	Java[2]	Chinese	10
		Javanese	1
Jaffe	Chicago	Whites	5
		Negroes	4
Socharto[3]	Java	Chinese	5
		Malay (Javanese)	1
Eagle & Gillman	South Africa	Europeans	3
		Eurafricans	1
		Bantu	0.4
Clark	Panama[4]	West Indian Negroes	5
Ruiz[5]	Argentina	Argentines	3

[1] Given in round figures. Uncorrected from authors' own data.

[2] Incidence for coolies (5 per cent) not included because based on too few autopsies.

[3] Cited by Bonne et al.

[4] Incidence for Latin Americans (2.6 per cent), and whites (2.3 per cent). Yellow race not included because of insufficient autopsies.

[5] Cited by Pavlovsky.

* No doubt a part of the uncertainty regarding geographic differences in the incidence arises from geographic variations in the character of the disease (178, 179). During the recent war, studies of peptic ulcer in military personnel were remarkably consistent in showing that gastric ulcers comprised 5 per cent or less of the total incidence in the American and Canadian forces, as compared with about 15 per cent in the British (150).

Gillman (25) (see Table 21). The reports of the former two authors leave no doubt that in the Netherlands Indies the disease is common among Chinese but very infrequent among Javanese. In South Africa (25), peptic ulcer is much more frequent in Europeans than in Eurafricans or in native negro tribesmen.

On the other hand, West Indian negroes working in the Panama Canal Zone (14) develop peptic ulcer with about the same frequency as whites in the United States. And, in Chicago (89), the disease occurred about equally in negro and white females,* while among males the whites showed a clearly greater incidence.† Moreover, Jaffe (52) asserted that peptic ulcer was more lethal in whites than in negroes.

Incidence of Gastric Ulcer

Chronologic Changes. Ulcer of the stomach was a common autopsy finding more than 100 years ago when the first postmortem survey was reported (16), and there is no clear-cut evidence of a progressive change in the incidence (Table 22). In regard to chronologic differences, the same comments are appropriate as were made for peptic ulcer as a whole. For

* I.e., according to Portis and Jaffe (89). But Jaffe (52) concluded that the disease was more frequent in negresses than in white females.

† This is in agreement with Rowntree's (174) figures on the incidence of peptic ulcer in selective service registrants:

	Peptic Ulcer Per Cent	*History of Peptic Ulcer, Per Cent*
White	0.52	0.42
Negro	0.14	0.09

On the basis of observations made in an Army General Hospital, Kirchner (175) concluded that the disease appeared with equal frequency in the two races under conditions provided by the armed forces. His data yield the following comparison for a one year period.

	Per Cent of Total Hospital Admissions	*Per Cent of Admissions to Gastrointestinal Section*
White	2.0	42.7
Negro	4.0	49.4

Table 22

INCIDENCE OF GASTRIC ULCER AT AUTOPSY

Observer	*Period*	*Place*	*Gastric Ulcer + Scar*				*Gastric Ulcer Alone*				*Remarks*
			♂	♀	T	Ratio ♂:♀	♂	♀	T	Ratio ♂:♀	
Dittrich	1844–46	Prague	..	..	8.5	..	..	..	2.9	..	RTAO 10
Willigk	1850–55	Prague	2.0	6.0	4.2	0.3:1	0.4	0.9	0.7	0.3:1	RTAO 10
Wollman	1866–67	Berlin (Charite)	3.5	4.1	..	0.9:1	..	..	..	..	CAPU
Hjelt	1858–69	Helsingfors	..	..	..	..	0.7	2.2	..	0.3:1	CAPU
Eppinger	1868–71	Prague	2.5	2.5	2.5	1:1	1.8	1.0	1.4	1.8:1	RTAO 10
Greiss	1873–78	Kiel	..	..	..	..	3.3	3.5	3.4	1:1	Adults over
Berthold	1868–82	Berlin (Charite)	2.1	3.8	..	0.6:1	1.2	1.5	..	0.8:1	CAPU
Cohn	1879–90	Kiel	5.3	22.2	11.2	0.2:1	1.5	3.1	2.1	0.5:1	Adults over
Stoll	1884–92	Zurich	1.7	2.5	..	0.7:1	..	..	..	..	CAPU
Schneider	1895–99	Munich	1.3	2.2	1.7	0.6:1	1.2	1.6	1.4	0.7:1	Adults over
Backman	1887–1900	Helsingfors	3.2	2.3	2.8	1.4:1	..	..	..	..	Adults over
Schädel	1876–1902	Munich	1.0	1.9	..	0.5:1	..	..	..	..	CAPU
Brinkmann	1890–1904	Kiel	7.8	29.7	14.6	0.3:1	2.7	5.5	3.7	0.5:1	Adults over
Wolowelsky	1895–1905	Basel	3.6	4.2	..	0.9:1	..	..	..	..	CAPU
Kirsch	1901–08	Munich	4.4	5.3	..	0.8:1	3.4	2.7	..	1.3:1	CAPU
Kossinsky	1895–1910	Erlangen	3.4	5.9	4.5	0.6:1	2.2	2.4	2.3	1:1	RTAO 10
Scheel	1907–10	Copenhagen	4.2	14.9	8.5	0.3:1	2.6	4.0	3.2	0.7:1	Adults over
Schmidtgall	1906–12	Leipzig	2.2	4.0	..	0.6:1	1.6	1.6	..	1:1	CAPU
Gruber	1899–1912	Munich	..	..	5.9	..	..	..	4.1	..	RTAO 10
Hart	1913–16	Berlin (Schöneberg)	5.3	9.3	7.2	0.6:1	2.7	2.7	2.7	1:1	Adults over
Musa	1919–20	Berlin (Schöneberg)	7.0	8.4	7.9	0.8:1	2.3	2.5	2.4	1:1	Adults over
Ophüls	1900–23	San Francisco	..	..	1.6	..	..	..	1.6	..	RTAO 15
Sturtevant & Shapiro	1904–22	New York	..	..	1.9	..	..	..	1.4	..	RTAO 10
Lehmann	1925	Vienna	12.5	17.1	14.8	0.7:1	3.0	1.3	2.0	2.3:1	74% Adults over 50
Stewart	1921–26	Leeds	..	..	4.3	..	2.0	2.6	2.2	..	CAPU
Jaffe	1929–34	Chicago (Cook County)	..	..	2.8	..	..	..	1.9	..	RTAO 10 corrected for erosio
Wright-Smith	1927–36	Melbourne	..	..	3.1	..	3.6	1.7	2.9	2.1:1	Adults over
Portis & Jaffe	1929–36	Chicago (Cook County)	3.0	1.9	..	1.6:1	2.5	1.4	..	1.8:1	CAPU
Hansen	1907–36	Copenhagen	3.8	5.7	4.7	0.7:1	..	..	..	..	Adults over

RTAO—Recalculated to Adults Over.
CAPU—Composition of Autopsy Population Unknown.
T—Total, male plus female.

example, Brooks (12) found only nine gastric ulcers and scars in 1(consecutive adult autopsies at Bellevue Hospital in New York in 1(Since 843 of the postmortem examinations were performed by Bro personally, and the remaining 157 by his two associates, it appears t the figure of 0.9 per cent gastric ulcers and scars is a reliable index of

idence of the disease at that time. If so, then the incidence (1.9 per cent) tained by Sturtevant and Shapiro (122) indicates that gastric ulcer has en on the increase at Bellevue. On the other hand, Howard (49) obned, at the time of the Brooks' (12) report, a figure of 1.4 per cent gastric er among 561 autopsies at the New York Hospital; if this figure means ything, then the incidence of 1.9 per cent for the period 1904–1922 (122) es not necessarily represent a clear-cut increase in the disease for New rk City.

The data for Philadelphia are equally unsatisfactory. McFarland (78) ted that ulcer of the stomach in the Philadelphia General Hospital med to be very rare, but he had no autopsy statistics to offer. Howard ') reported seven ulcers in 547 postmortems at the Pennsylvania spital and three in 279 at the University Hospital, yielding a total idence of 1.2 per cent. Francine's (29) figure from 2830 autopsy records the Philadelphia Hospital (Blockley) for the period 1893–1902 was per cent; Gordon and Manning (34) obtained the same figure in their vey at the Philadelphia General Hospital for the years 1920–1937. It ght seem that there has been no change in the frequency of gastric ulcer Philadelphia, but these data do not permit that assumption because ne of the reports from that city are statistically acceptable. The only ng we can conclude is that the lesion was not rare, as McFarland ught, 50 or 60 years ago.

In 1857, Brinton (10) placed the incidence in Europe at about 5 per t. Lebert (65) wrote: "I believe I am not going too far astray when I mate the average frequency of gastric ulcer in Europe at about 4 per t for autopsy material." Comparable modern figures are those of vart (120), who noted *gastric* ulcers and scars in 4.5 per cent of 1500 opsies studied intensively for gastroduodenal pathology, and of Hansen), who obtained an incidence of 6 per cent in a survey of 21,200 opsies in which only proven peptic lesions were accepted.

The Berlin data of Hart (44) for the years 1913–1916 and of Musa (76) 1919–1920 show an incidence of 7 to 8 per cent, or more than double reported from Berlin by Wollmann (134) and Berthold (6) for the od 1866–1882. But there are a number of reasons why the reported erence cannot be accepted unreservedly as evidence for an increase ne frequency of gastric ulcer in that city. For one thing, the data of the ier authors is incomplete; for another, the modern survey was made ne Schöneberg Hospital, and the older one at the Charite. Experience shown that, among different institutions, there are often wide varias in the methods of postmortem examination, the criteria for the tification of peptic lesions, and the completeness of the autopsy ocols.

Furthermore, there is the question of the accuracy with which a give hospital's autopsy material mirrors the occurrence of a particular disea in the population at large. An example of such a difference has alread been cited in the comparison of two Chicago surveys. And finally, it mu be noted that whereas Hart (44) and Musa (76) made a particular searc for scars, the prior Berlin pathologists did not. Or, as Oberndorfer (81 put it in commenting on the apparent rise in the autopsy incidence gastric ulcer in Munich, "the earlier Munich pathologists did not do thorough an examination of the stomach." In this connection, it is not worthy (Table 22) that in all the surveys which yielded a relatively hig figure for the incidence of peptic gastric lesions, the number of sca greatly exceeded the number of open ulcers.

Geographic Differences. In 1885, Welch wrote: "The disea (gastric ulcer) seems to be somewhat unequal in its geographic distrib tion, but the data bearing on this point are altogether insufficient." that time, while systematic autopsy surveys were being reported fro Prague, Berlin, and Munich, only fragmentary observations were bei made in the United States.

Keating (56), demonstrating to the Philadelphia Pathological Socie the autopsy specimen from a case of perforated gastric ulcer, sai "Judging from the few cases which have been reported, its occurren must be far rarer than in England or on the continent of Europe." Accor ing to McFarland (78), Osler stated that among the first 1000 autops at Johns Hopkins Hospital there were but nine gastric ulcers. An identi figure was obtained by Brooks (12) at Bellevue. Thus, there is good pr sumptive evidence that the disease was distinctly less common in t country than in Europe 50 years ago. To what extent this holds tr today is not entirely clear, because now that we have started maki autopsy surveys of peptic ulcer in the United States, we have not be getting reports on this subject from Europe. However, on the basis of t data as it stands in Table 22, peptic gastric lesions are hardly more th half as frequent in this country as in Europe, and the difference lies m in the incidence of scars than in open ulcers.

There has been much speculation among German authors on t causes of the differences in the incidence of gastric ulcer in various Eu pean countries and even in different sections of the same country. But m of this discussion has been wasted; the alleged differences were n confirmed. Sperk (115), in 1867, reported that "round stomach ulc was very frequent in East Siberia and discussed the climatic and diet factors in that region, but his observations were not supported by a sin digit of data. Von Sohlern (113), in attempting to make a case for

uence of nutrition on the development of gastric ulcer,* pointed out t Dr. Petersen saw only three gastric ulcers in 6000 autopsies which he formed at the Alexander Hospital in St. Petersburg. This would be the est incidence (0.05 per cent) ever reported anywhere, if it were true. t this figure is rendered doubtful by the results of Sommerfeld's (114) vey at the same hospital from 1891 to 1911, yielding an incidence of per cent.

Korczynski and Jaworski (59) stated that in 1886 Professor Browicz nd only two gastric ulcers in 820 bodies examined at the Pathological titute in Krakow. They therefore postulated that the inhabitants of this ion were protected against ulcer by a higher alkalinity of the blood, ived from the carbonates of their predominantly plant diet. Yet zinski (31), in a survey embracing 11,000 autopsies at the same itution for the years 1890–1900, obtained an incidence three times as h as that reported only a few years previously. Surely the dietary ctices of these people could not have changed sufficiently to account the increase. It is more likely that the incidence of gastric ulcer was not ow as the earlier and less intensive observations indicated. Even then, zinski's figure of 0.7 per cent gastric ulcers and scars was significantly er than that reported from German cities during a comparable period. it did correspond to the figure quoted for the United States, where the ary habits apparently were not sufficiently distinctive to be invoked factor contributing to the low incidence.

This is not to imply that we negate the role of nutrition in the etiology astric ulcer, but only to point out that the evidence as supplied by the ilable autopsy statistics of the incidence is not convincing.

Racial Differences. As for racial differences in susceptibility to ric ulcer (Table 23), there is even less autopsy data than for peptic r as a whole. This is because some of the authors reporting on race dence did not break down their figures according to the site of the n.

According to the figures of Portis and Jaffe (89), gastric ulcers were e as frequent in whites as in negroes among males, but approximately

He postulated that the predominantly vegetarian diet of the Russians increased potassium content of the blood and thereby afforded protection against hyper- tion and ulceration of the stomach. No experimental evidence was adduced (a) the blood potassium was higher among Russians than among other nationals, (b) the blood potassium level affected gastric secretion, or (c) that less gastric juice ecreted by Russians than by others. According to Riegel (94), Westphal found the ty elevated in one out of every three or four Russian patients who had stomach nts; and in the province of Upper Hesse, where the inhabitants ate very little , hypersecretion and ulcer were common.

Table 23

RACIAL DISTRIBUTION OF GASTRIC ULCER AT AUTOPSY

Observer	*Place*	*Group*	*Incidence*	
			Gastric Ulcers and Scars Per Cent	*Ulcers Only Per Cent*
Yamagiwa.....	Tokio	Japanese	14	4
Yukawa.....	Tokio	Japanese	..	2
Kouwenaar.....	Java	Chinese	8	..
Socharto.....	Java	Chinese		3
		Malay (Javanese)		0.3
Vint.....	Nairobi (East Afr.)	Negro	0.05	..

equal among females. The difference between white and negro males not true of death rate (p. 612, Table 101).

Yukawa (139) obtained an autopsy incidence of 1.9 per cent in Tok and quoted Yamagiwa as having reported 14 per cent in a survey whi included the smallest scars. In the latter study, the original publicati of which is not available to us, open ulcers occurred in 4 per cent of t bodies examined.* Thus, there was too much difference in the figures the two Tokyo observers to permit an estimate of the probable incide of the disease among the Japanese.

Kouwenaar (61) found gastric ulcers or scars in 8 per cent of Chin autopsied in Java, whereas Socharto (see Bonne et al. (7)) noted lesions in 3 per cent. Both observers reported that the disease was r among the Javanese in the same locality.

Vint (126) stated that the only peptic lesion noted by him in 1 autopsies in Nairobi, East Africa, was a healed gastric ulcer.

CHANGES IN SEX INCIDENCE. Most of the older texts stated categoric that gastric ulcer affected women more frequently than men. For exam Pye-Smith (90) wrote, "All writers are agreed that it occurs more ofte females than in males." Although occasional authors (13, 40, 55) obtai figures which led them to question this rule, autopsy studies (Table generally indicated an unequivocal predominance of peptic gastric lesi among females.

To what extent the sex incidence of gastric ulcer has changed may illustrated by comparing the reports prior to that of Wolowelsky (1 with the subsequent ones. Such a dividing point is convenient beca

* And, according to Kouwenaar (61), in 5.3 per cent of those aged 20 or more

lowelsky's survey embraced the decade straddling the turn of the tury.

In the earlier period, females generally predominated in the frequency ılcers plus scars and of ulcers alone. In the more modern series of veys, there have been only two reports in which females had the greater centage of open ulcers, but, up to the time of Portis and Jaffe's (89) ly, the incidence of ulcers plus scars continued to be higher in females. us, there has been a definite reversal of the sex ratio of open gastric ers and, if the findings of Portis and Jaffe are representative of the

Table 24

RATIO OF ULCERS TO SCARS

Observer	*Period*	*Place*	*Ratio of Gastric Ulcer : Scar*		*Ratio of Duodenal Ulcer : Scar*	
			M	*F*	*M*	*F*
ch	1844	Prague	2.1:1	0.8:1	..	..
ich	1844–46	Prague	0.5:1	0.3:1	..	..
gk	1850–55	Prague	0.3:1	0.2:1	3:1	3:1
nger	1868–71	Prague	3:1	0.7:1	..	..
s	1873–78	Kiel	0.8:1	0.2:1	..	..
hold	1868–82	Berlin	1.4:1	0.7:1	13:1	6:1
h	1879–90	Kiel	0.4:1	0.2:1	..	..
eider	1895–99	Munich	16:1	2.5:1	6:1	6:1
løf	1896–1902	Copenhagen	2.8:1	0.6:1	..	..
h	1901–08	Munich	3.6:1	1:1	18:1	6:1
el	1907–10	Copenhagen	1.6:1	0.4:1	2:8:1	2:1
idtgall	1906–12	Leipzig	2.6:1	0.7:1	..	..
nsky	1895–1910	Erlangen	1.9:1	0.8:1	21:1	6:1
agiwa	1911	Tokio	0.3:1	0.5:1	..	..
mann	1890–1904	Kiel	0.5:1	0.2:1	..	..
	1913–16	Berlin (Schöneberg)	1.1:1	0.4:1	0:8.1	0.7:1
	1919–20	Berlin (Schöneberg)	0.5:1	0.4:1	0.8:1	0.4:1
er & Kratzeisen	1917–22	Mainz	4:1	1.6:1	2.2:1	3.5:1
ann	1925	Vienna	0.3:1	0.1:1	0.6:1	0.2:1
en	1907–36	Copenhagen	2:1	0.8:1	4.7:1	3.1:1

nt status of peptic gastric lesions, then it appears that the reversal has recently extended to scars.

rom the data in Table 22, it is difficult to identify, with any enthu- c conviction, the precise nature of this apparent reversal; however,

the work of Hansen (42) suggests strongly that the autopsy incidence of open ulcers has been decreasing in females while remaining more or less unchanged in males.*

It would be enlightening if we could obtain from the data some acceptable indication of the changes, if any, in the incidence of scars, but this is not possible. For example, the ratio of gastric ulcers to scars has been computed (Table 24) for each sex. No consistent trend is discernible. This tabulation only reaffirms the fact that in females there have hitherto occurred more scars than open ulcers, while in males the reverse has usually been the case. Hence it has always been held that gastric ulcer has a greater tendency to heal in females—an opinion which is open to question.

The evidence relating to the severity of the disease as it affects opposite sexes may represent another aspect of a progressive change in the sex incidence, or it may amount to no more than another example of conflicting observations. In the older literature, Welch (127) stated that "perforation is a more common event in females than in males" (footnote, p. 483); whereas Pye-Smith (90) noted more fatal cases in men than in women. Fenwick and Fenwick (28) concluded from their autopsy studies that acute gastric ulcer, i.e., the rarely fatal form of the disease, occurred almost exclusively in young females, while the chronic ulcer was more frequent in males. The data of Hurst and Stewart from this century (50) showed "a change from male predominance in respect of acute ulcer to female predominance in respect of chronic."

Stoll (121) in 1892 believed that there was a significant sex difference in the location of gastric ulcer. He noted that in males the lesion exhibited a predilection for the "pars pylorica and pylorus"; in females, for the lesser curvature. Lehmann (66) in 1925 made a similar observation; he cited, as an illustrative point, a ratio of 40 scars on the proximal third of the stomach to one on the distal third. The data of Hansen (42) collected from 1907 to 1936 show that in both sexes the site of predilection is the corpus of the stomach, but in males, there is a greater proportion of lesions in the antrum and at the pylorus.

That the ratio of lesions in the antrum to those in the corpus has exhibited a tendency to increase is illustrated by the following figures recalculated from Hansen (42):

* Alsted (1) interprets his clinical statistics as indicating that "the frequency of fresh ulcers is unchanged in the course of years for men, but rapidly decreasing for women." He shows that peptic ulcer manifests greater chronicity now than in former times; and on the basis of these considerations he summarizes the sex trend as follows: "(a) For men: *nowadays no more get ulcers than previously, but there are more who have them;* (b) For women: *fewer and fewer get ulcers, and fewer and fewer have them.*"

	Male			*Female*		
	Corpus	*Antrum*	*Total*	*Corpus*	*Antrum*	*Total*
1907–16	2.5	1.2	3.7	10.1	0.6	10.7
1927–36	2.5	1.8	4.3	3.4	0.8	4.2

The increasing ratio of antral lesions in males is due to an absolute increase in antral lesions; in the female, the changed ratio is due to a marked reduction in corpus lesions.

Age Incidence. Autopsy data is generally considered to be of little value as a source of useful information on the age incidence of peptic ulcer, because the age at death is usually not directly related to the presence of the ulcer, whether open or healed. Nevertheless, there are certain points of interest in the age distribution of gastric ulcer in autopsy material in Table 25. This tabulation takes into account only those reports in which

Table 25

Age-sex Incidence of Peptic Gastric Lesions at Autopsy

Showing the age decades of principal frequency; where the incidence was relatively high throughout more than one decade, the decade of highest incidence is shown in **boldface type.**

Observer	*Male*			*Female*		
	Ulcers	*Scars*	*Ulcers + Scars*	*Ulcers*	*Scars*	*Ulcers + Scars*
Willigk (1852)	..	..	7	..	..	3, 4, 6, 7, **8**, 9
" (1854)	..	..	6, 8	..	..	3, 4, 5, 6, 7
Eppinger (1872)	..	..	5, 6	..	..	5, 6, 7, **8**
Greiss (1879)	6	8	..	6	8	..
Cohn (1891)	7	7	..	6	7	..
Scheel (1912)	..	..	5, **6**, 7, 8	..	..	3, 4, 5, 6, **7**, 8
Kossinsky (1913)	7	8	..	5, **8**, 9	6, **7**, 8	
Brinkmann (1915)	**7**, 8	7, 8, **9**	..	3, 4, **6**, 8, 9	5, 6, 7, **8**, 9, 10	..
Gruber & Kratzeisen (1924)	5, 6, 7, **8**	7, 8	..	6, 8	7	..
Lehmann (1926)	6	7, 8	..	6, 7	6, 7, **8**	..
Jaffe (1935)						
Whites	..	..	4, 5, 6, **7**, 8	..	..	**7**, 8
Negroes	..	..	4, 5, 6, **7**	..	..	4, 5, **6**, 7, 8

the frequency was based on the number of individuals in the respe decades; numerous data had to be excluded because the age incidence improperly calculated (see p. 456).

The point of greatest importance in respect to the age incidenc gastric ulcer is its relative infrequency in the first two decades of Hurst and Stewart (50) noted acute ulcers in 1.6 per cent of 367 indivi dying in the second decade, but this figure includes erosions. Gastric as such is rare in this age group.

While it is true that the presence of a gastric ulcer or scar at mortem provides no information regarding the age of onset of the l the data in Table 25 show that up to the fifth decade the lesion is more frequently in female cadavers than among male. This is cons with the clinical observation that the age of onset of gastric ulce generally been lower in women. However, accompanying the sex re in incidence, the survey by Hansen (42) indicates an increased freq among the lower age groups in males.*

Another instructive aspect of Table 25 is the consistently high inci of peptic gastric lesions in the later years of life. The predominance of gastric ulcers among individuals in the sixth to eighth decades co three significant clinical observations: (a) The disease is one of poten great chronicity; (b) the presence of an unhealed ulcer in the stom an elderly individual does not necessarily signify cancer (see, espe Bockus (141)), (c) with the progressively increasing life expectancy, more people live to age 70, gastric ulcer will actually be more prev even though the incidence may not increase.

Incidence of Duodenal Ulcer

Chronologic Changes. One hundred years ago duodenal ulc rarely described in autopsy protocols (Table 26). For example, the P reports of 1850 to 1855 showed only one duodenal ulcer per 1000 au Whether such figures represent the true incidence or whether the was present oftener than it was reported cannot be determined w certainty.

* Changing age incidence of gastric ulcer in males as calculated from M data:

	20–29	30–39	40–49	50–59	60–69	70–79	80–89
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 26

INCIDENCE OF DUODENAL ULCERS AT AUTOPSY

Observer	Years	Place	Duodenal Ulcers + Scars			Duodenal Ulcers Alone			Remarks
			M	F	Total	M	F	Total	
[illegible]	1850–55	Prague	Only one scar			0.1	0.1	0.1	RTAO 10
[illegible]	1866–67	Berlin (Charité)	No scars		..	0.3	0	*	CAPU
[illegible]	1868–71	Prague	No scars		..	0.2	0.2	0.2	RTAO 10
[illegible]	1894–82	Berlin	0.2	0.2	..*	0.2	0.2	..*	CAPU
[illegible]	1893–99	Munich	0.2	0.4	0.3	0.2	0.3	0.3	Adults over 15
[illegible]	1878–1901	Basel	0.8	0.6	..*	..	..	..	CAPU
[illegible]	1901–08	Munich	0.9	0.9	..*	1.0	0.8	..*	CAPU
[illegible]	1895–1911	Erlangen	1.0	0.6	0.8	0.9	0.3	0.6	RTAO 10
[illegible]	1907–10	Copenhagen	1.2	0.2	0.8	0.9	0.2	0.6	Adults over 20
[illegible]	1899–1913	Munich			0.8			1.4	Adults over 20
[illegible]	1913–16	Berlin (Schoneberg)	5.3	4.4	4.9	2.3	1.7	2.0	Adults over 16
[illegible]	1919–20	Berlin (Schoneberg)	8.5	3.3	5.4	3.9	0.9	2.1	Adults over 16
[illegible]	1925	Vienna	7.3	6.7	7.0	2.5	1.0	1.6	74% adults over 50
[illegible]	1900–1923	San Francisco	..	..	1.1	..	..	0.9	Adults over 15
[illegible] & [illegible]	1904–22	New York	..	..	0.7	..	..	0.6	RTAO 10
[illegible]	1923	Leeds	..	..	5.8	..	..	..	CAPU
[illegible]	1923–34	Chicago	..	..	1.8	..	..	1.5	RTAO 10
[illegible] & Jaffe	1923–36	Chicago	2.9	1.1	..	2.2	0.8	..	CAPU
[illegible]	1927–34	Melbourne		..	2.6	3.2	1.5	2.6	Adults over 14
[illegible]	1907–34	Copenhagen		..	1.1	..	..	0.9	Adults over 15

[illegible]

t and Stewart (50) thought that the duodenum was not usually d thoroughly except in cases of burns because ulcers were not y considered to occur there. This impression is supported by the many authors dealing with "simple ulcer," "round ulcer," e ulcer," or "peptic ulcer" ignored the duodenum completely. 53) stated that in confirmation of Curling's interesting observa- de in 1842 he found duodenal ulcers in two burn cases, but beyond nanifested no interest in duodenal ulcer, in contrast to his careful peptic lesions of the stomach. Still, Rokitansky (98), a few years 839), described only six duodenal lesions out of a total of 79 peptic ranting a 5 per cent incidence for gastric ulcer, this would mean nately 0.4 per cent duodenal ulcers; thus, the findings of this very nd thorough observer would correspond to the incidence as

estimated by Perry and Shaw (86) from an examination of
mortem records (1826–1872). L. Mueller (74), it is true, in 18
a higher proportion—10 duodenal ulcers among a total of
ulcers—but we have no idea what kind of lesions he was de
Wollmann (134), on the basis of a survey of the material at
Institute, concluded in 1868 that duodenal ulcer was "quite i
Oppenheimer (83), at about the same time, made a special s
disease and argued that "these ulcers are not so infrequent as
supposed," but he did not present adequate data to support

Prior to 1900, only two surveys were made specifically to de
incidence of duodenal ulcer. Perry and Shaw (86) found th
scars of the duodenum were recorded in 0.4 per cent of 17,
protocols covering the years 1826–1872. Fenwick and Fe
obtained a figure of 0.26 per cent in 13,055 autopsies *in which*
of the duodenum was noted. Both of these reports were based
necropsy material, and it is therefore the more puzzling that th
derived only from records in which the duodenum was menti
be lower than that derived from all of the necropsy records
period of years.

Fusterman and Balfour (27) believe that the increased a
dence of duodenal ulcer is due in part to a better recognition of
duodenum. There is evidence both pro and con. Berthold
presumably expressed the view of Virchow's group when he
scarring of duodenal ulcer practically never occurs. This
voiced at a time when scars were certainly well recognized in
and one is inclined to think that, had scars occurred in any
numbers in the duodenum, they would not have been
overlooked.

Grünfeld (39) in 1883 made a special search for scars, yet
four cases of healed duodenal ulcer in 1150 autopsies in which
That the London pathologists of the Nineteenth Century we
the occurrence of scars is indicated by the fact that Perry and
70 cases of duodenal ulcer included eight scars.

However, as pointed out below, there is evidence that ma
gists overlook all but the most obvious scars of the duodenum.
reported where these lesions are not under special scrutiny.
(47), who reported that scars were present as frequently as
series of autopsies in which the duodenum was examined (and
wrote: "The question arises, why have these scars been ha
usually unknown? In my opinion the explanation lies in the
fact that even today in many institutions, the duodenum is
examined." It is evident from Table 2b that, in the surveys

and Lehmann (66), who made a special search for scars, the d healed lesions materially exceeds that of open ulcers. But, ser lesions have been reported in generally increasing fre- due to the incidence of duodenal ulcers cannot be attributed ed recognition of scars. That is, even when scars are left out riations, there is a definite trend in the direction of a higher uence of the disease. In fact, the above named authors are , who found a marked excess of scars over open lesions.

26, Column 2, it appears that the incidence of open duodenal es falls into three distinct periods: (1) prior to the turn of the e the disease was noted to run from 0.1 to 0.3 per cent of au- around the turn of the century, when the incidence was to about 1 per cent; and (3) subsequent to 1913, when the ged from 2.2 to 3.9 per cent. In the light of these figures, it is at the question has been propounded: "Was the increase in er due to the work of Moynihan?" In other words, was the d recognition rather than of occurrence? There are a number ons which compel us to take the stand that the increase was apparent:

ficult to believe that pathologists like Rokitansky, Virchow, others either did not recognize the anatomic dividing line stomach and duodenum, or that they failed to examine the overlooked ulcers when present.

ngue publicized duodenal ulcer in this country early in the ry, yet the autopsy surveys totaling 85,126 cases which cover hat era show a comparatively low incidence of the disease. nical incidence has never been, and still is not, an index of ncidence. For example, duodenal ulcer is clinically much t than gastric ulcer in geographic areas where an post- incidence is roughly equal. Therefore, better recognition of n influence the clinical incidence to a much greater extent fluence the autopsy, or theoretically the true, incidence. This ach is overlooked by clinicians who doubt the validity of the es when the latter do not conform to their own clinical

ce, von Bergmann (4) argued as follows:

ge of the Sons Moynihan appeared, when the Mayo brothers reported when Soupault stressed the pyloric syndrome as a sign of duodenal rhoncus on stomach disease, as in Germany, Ewald and many others, e overdrive with stenosis. They sought geographical reasons why it America and England than here; they argued about anatomical explained that duodenal ulcers are gastric or in any case pyloric ulcers

and that the limits of the stomach are erroneously determined by the operators. They did not want to understand that thousands and more thousands of cases had gone under wrong diagnoses and that they must profoundly relearn. As late as 1912, when Bier embraced the other opinion on the basis of his own experience as a surgeon, Ewald still thought that the frequency of duodenal to gastric ulcer was as 1:45, and even that was considered by many to be a concession. They thought they were supported by pathologic anatomy, since almost without exception all pathologists affirmed the infrequency of duodenal scars. I was able, with my collaborators Katsch and Westphal, as one of the first in Germany, to publish as early as 1913 50 cases of duodenal ulcer clinically well observed and for the most part verified by operation. The anatomists came last. Particularly Hart, also Rössle and Gruber produced the anatomic evidence that among us the situation was nothing other than reversed.

Surely Bergmann could not have intended his remark "the anatomists came last" to mean that, while the surgeons were able to recognize a duodenal ulcer at operation and the internists were able to diagnose it clinically, the pathologists were unable to identify the lesion at the autopsy table. The anatomists "came last" only in the sense that instead of making annual surveys of the incidence, they were making surveys generally covering about a decade at a time, so by the time the autopsy reports appeared in the literature, the clinical increase was already apparent. The fact is that almost all of the German postmortem statistics dealing with material in the first decade or so of the present century showed a distinct rise in the proportion of duodenal ulcer cases. Unfortunately, the rate and extent of this rise was overlooked because of incomplete statistical treatment of the autopsy findings, as will be apparent from what follows.*

d. Whatever impetus Moynihan may have given to the search for duodenal ulcers at autopsy could at best account only for the relatively sudden rise in autopsy incidence during and shortly following the propagation of his teachings. It could not account for a continuing increase up to the present day (1936). As was noted before, the data on the nature and rate of the increase were not wholly satisfactory, although suggestive, until Hansen (42) recently reported his exhaustive survey made in Copenhagen.

We have prepared from Hansen's data (42) a compilation which clarifies the picture of the changing incidence, at least as it pertains to

* Still, Ihre and Müller (144) consider it probable that a number of clinically diagnosed duodenal ulcers are being missed at autopsy. They state: "Great care is required in autopsy examination to find the many times insignificant ulcer scars which in roentgen examination show typical deformation of the duodenal bulb, and small superficial mucosal ulcers which cause a characteristic roentgen picture are often impossible to find on postmortem examination." This is a moot point, but it is susceptible to further investigation.

conditions in Denmark. The accompanying tabulation shows that during a 30 year period from 1907 through 1936, the frequency of duodenal ulcer in the third decade age group increased five-fold, in the fourth decade four-fold, in the fifth decade three-fold, and in the sixth decade two-fold.

Table 27

CHANGES IN THE PERCENTAGE OF AUTOPSY MATERIAL AND DUODENAL ULCER*

Period	*Total Male Autopsies*	*Age 20–29*		*Age 30–39*		*Age 40–49*		*Age 50–59*	
		Per Cent of Autopsies	*Incidence of D.U.*	*Per Cent of Autopsies*	*Incidence of D.U.*	*Per Cent of Autopsies*	*Incidence of D.U.*	*Per Cent of Autopsies*	*Incidence of D.U.*
1907–16	2572	9	0.9	14	1.4	20	1.0	26	1.5
1917–26	4255	6	2.4	11	2.6	19	1.6	25	0.9
1927–36	4496	3	4.5	6	5.9	16	2.9	23	3.3

* Calculated from data of Hansen (42) (Copenhagen, 1943).

This remarkable increase, which parallels clinical observations, has not been hitherto apparent because all previous autopsy surveys have failed to take into account the significance of the age distribution of the autopsy population. The reason why the overall increase in autopsy incidence of duodenal ulcer has not been so marked is apparent from the changes in autopsy rate in the respective age groups. In the 30 years covered by Hansen's study, the proportion of 20 to 29 year olds in the autopsy material fell from 9 per cent to 3 per cent; i.e., the age group in which the incidence rose to five times its previous rate came to comprise only one third as much of the total autopsy material. In the 30 to 39 age group, the incidence of ulcer quadrupled itself, but this group at the same time fell to less than half its previous share of the autopsy population. Meanwhile, in the age group from 60 years upward, in which the incidence of duodenal ulcer had not changed during the latter two decades of this survey, the proportion of autopsies was increasing. Thus, the effect of the increasing number of duodenal ulcers in younger people is diluted in autopsy material by the relatively increasing number of autopsies on older individuals.

On this basis, *the only way to compare autopsy incidence in different reports is to correct for the age-sex distribution.* A less laborious method is to compare the incidence in a given age-sex group; the appropriate calculations can be made for *only three* of the available autopsy reports, viz.:

Incidence of Duodenal Ulcer in Males During Fourth Decade of Life	
Schecl	(1867–80)
Gruber and Kratzeisen	(1917–22)
Portis and Jaffe	(1929–37)

The trend is definitely suggestive, but not as reliable as that Hansen's data.

c. Duodenal ulcer was practically unknown in either the A British armed forces during the First World War (1914–1) whereas it was the major cause of disability in the Second (1 (150). Schindler (151) and others have implied that in the earl real incidence was unrecognized because of lack of accurate methods. This could not explain the difference, unless one as most duodenal ulcers were formerly asymptomatic, in view of th the *incidence of dyspepsia* during the first World War was so low a very little notice in the army medical records.

All in all, it is difficult to support any view other than the been a distinct, progressive increase in the incidence of duod from the time it was first recognized until the present. We Jennings (54) when he writes: "After spending a great deal of t ing over English and German autopsy records of the 19th cen convinced that the older pathologists did not miss duodenal ul them pyloric and prepyloric in the lighthearted way often them; but it is difficult to convey this conviction to anyone else to us that if one adheres to the belief that "the cause of duodenu Berkeley Moynihan," then one might also assume that gastro not occur as frequently as duodenal ulcer, despite what the say, because Moynihan (181) stated in 1932: "Intrusions of into the abdominal cavity have, however, shown that gastr comparatively infrequent."

Geographic Differences. As was the case with gastric cannot obtain from existing autopsy reports a clear picture graphic and racial differences in the incidence of duodenal ulce it is practically certain from other evidence that such differen However, the available data do not support the view that the of this disease is dependent upon the level of civilization.

Back in the days when duodenal ulcer was only occasionall in American and European autopsy material, White (128) Punjab that Indian natives "do suffer frequently from duod ulcer." If this communication is accepted as representing the the more recent observations of McCarrison (77), Degra (25) regarding the high incidence of duodenal ulcer in certain

not indicate a new development, i.e. one attributable to the modern civilization. (Nor do observers in India so regard it.)

Table 28

...ence and Racial Distribution of Duodenal Ulcer at Autopsy

Observer	Place	Group	Incidence	
			Ulcers + Scars	Ulcers Only
.....	Berlin	Germans	4.9	2.0
.....	Leeds	English	5.8	3.8
.....	Chicago	Americans	2.5	1.7
.....	Melbourne	Australians	2.6	2.6
.....	Vienna	Austrians	7.0	1.6
.....	Java	Chinese	..	1.8
		Javanese	..	0.5
.....	Java	Chinese	3.5	2.1

...ng to Table 28, duodenal ulcer appears to be more frequent in ...an on the continent or elsewhere. But there are certain con- ... which render it extremely doubtful whether this difference is ...e first place, the statistics of Stewart (120) are based on autopsy ... the Leeds General Infirmary, which was apparently a mecca ...l ulcer cases because of the work of Moynihan. Therefore, the ...psy material was probably not a fair sample of the population ... We cannot state this as a certainty because of the surprising ...ewart's has been the only published systematic autopsy survey ... ulcer in England in the past 46 years; hence, there are no ...h data which could serve as an acceptable basis for comparison. ...r, there is good presumptive evidence that the Leeds statistics ...t representative of conditions throughout England than are the ...c figures (96) an indication of the incidence of duodenal ulcer ...d States. For example, White (129), in discussing Moynihan's ...r, stated that at Guy's Hospital in London during the period ... the incidence of open duodenal ulcers at autopsy was 1 per ...reat increase since the report of Perry and Shaw, from the same ...s attributed to the fact that patients were being sent to the ...o previously were not because the disease had formerly been ... necessarily fatal once the symptoms appeared. Still, the ...opsy incidence of 1 per cent is a far cry from the Leeds figure ...ent. Furthermore, according to Raw (92), in the 12 years ...10 there were 13 duodenal ulcers in 5000 autopsies at Liver- ...idence of 0.26 per cent.

It is apparently on the basis of these findings that Barclay (3) writ "There seems to be a geographical variation in incidence: at one ti duodenal ulcers were common in Leeds (where Moynihan was doing pioneer work on this condition), comparatively rare in Manchester, fo miles away, and almost unknown in Liverpool, eighty miles away—n only in the operating theatre but also in the postmortem rooms." It see to us that this is drawing the geographic distinction much too fine. perusal of the protocols of Moynihan's (181) surgically treated duoden ulcer cases reveals that while it is true only a few were referred fro Manchester, yet less than 30 per cent of the patients were residents Leeds. And anyway, the frequency of operation is not so much an ind of the incidence of duodenal ulcer as of its recognition. In any case, t implication remains that the incidence at Leeds is not the incidence England; at least, it should not be accepted as such until further surve are forthcoming. (See Clinical and Mortality Statistics in Chapter 17.)

Wright-Smith's (138) report of 2.6 per cent duodenal ulcers in M bourne appears to be based on a careful study, and it is therefore s prising that only two duodenal scars were noted in 4,085 autopsies. T would indicate a high incidence of the disease, with marked chronicit additional studies from Australia are therefore particularly desirable.

Racial Differences. The remaining data in Table 28 show significant differences in the incidence of duodenal ulcer among the raci groups indicated, except for the Javanese natives, in whom the autop rate of the disease is very low (0.5 per cent according to Socharto (s Bonne et al. (7)) and Kouwenaar (143)).

Portis and Jaffe (89) found a higher incidence of duodenal ulcer white males than in negro males, whereas the incidence among females the two races was the same.

Perhaps a good indication of the role of civilized life in the etiolo of duodenal ulcer would be provided by data on the incidence of t disease among native African negro tribes. The findings of Eagle a Gillman (25) leave no doubt that the lesion is rare among South Afric Bantus. In East Africa, Vint (126) did not observe a single instance duodenal ulcer among 1800 autopsies performed at Nairobi, but repo from Zanzibar (125) and Uganda (95) indicate that the disease is n uncommon among certain East African natives, although no autop statistics were presented.

Sex Incidence. At autopsy, duodenal ulcer is seen from two to f times oftener in males than in females. The indications are that the disea has always occurred more frequently in men than in women, in contr to the changing sex incidence of gastric ulcer.

Perry and Shaw (86) obtained a ratio, in cases excluding burns, three males to one female, and, although the sex composition of the autop

aterial was not recorded, it is not likely that there were three times as any male cadavers as female. Among Krauss' (62) collected cases, there ere 58 males and 6 females; Oppenheimer (83) found that among 79 ases in which the sex was recorded, 56 were males and 23 females. The ght cases of perforated duodenal ulcer presented by Dieulafoy (21) were l in males. Without including the many additional examples which ould be cited, it seems sufficiently clear that, although there were no ccurate autopsy statistics prior to the present century, duodenal ulcer as always shown a greater predilection for the male sex.

Whether there has been a change throughout the years in the extent to hich males predominate cannot be determined with certainty, although ie data (Table 26) convey the impression that there has been no striking hange in the sex ratio of the disease. Generally, the autopsy rate of uodenal ulcer appears to have increased among women *pari passu* with ie increased incidence in men.*

Table 29

AGE INCIDENCE OF PEPTIC DUODENAL LESIONS AT AUTOPSY
(Decade of highest incidence in **boldface**)

Observer	*Decades of Principle Incidence*
Scheel (1912)	**4**, 5, 6, 7, 8
Gruber & Kratzeisen (1924)	**3**, 5, 6, 7, 8
Sturtevant & Shapiro (1926)	**3**, 5, 6, 7, 8
Wright-Smith (1937)	3, **4**, 5, 6
Portis & Jaffe (1938)*	**4**, 7, 8

* Data for white males only.

AGE INCIDENCE. It is noted in Table 29 that duodenal ulcers are most mmonly found at autopsy in individuals of the third and fourth decade;†

* Alsted (1) holds that the increase has been more marked in males, and his opinion trongly supported by the data of Hansen (1943), who found that in males the inci- ice rose from 1.0 per cent in the decade 1907–16 to 2.1 per cent during 1927–36. females, the incidence remained at approximately 0.5 per cent.

† Schmidt (106) asserted that duodenal ulcer was principally a disease of infancy. m his autopsy survey at Breslau (1906–1913), he concluded "that ulcer rotundum deni is far more frequent during the first year of life than at any other age. This fact that I have not found in any previous statistical survey."

We might add that we have not found it in any subsequent one either. For ex- ple, Paterson (177) reported two cases of acute duodenal ulcer in 370 autopsies of nts under one year. More recently, Benner (105) found seven duodenal ulcers in consecutive autopsies on infants and children. One of the most extensive series rted was that of Holt (80), who obtained an incidence of 0.2 per cent duodenal rs in 1800 infants.

this is generally lower than the autopsy age group affected by gastric ulc Moreover, the lesion is recorded in significant numbers in the lat decades, unhealed as well as healed. Both of the above observations are accord with clinical experience.

Ratio of Gastric to Duodenal Lesions

If the incidence of gastric ulcer has remained generally unchang while duodenal ulcer has been on the increase, then the ratio of gastric duodenal peptic lesions (GU:DU ratio) should be expected to exhibi progressive fall. This is beautifully demonstrated in Table 30, especia

Table 30

Ratio of Gastric to Duodenal Lesions at Autopsy

Observer	*Period*	*Place*	*Gastric: Duodenal Ulcers + Scars*		*Gastric: Duode Open Ulcer*	
			M	*F*	*M*	*F*
Willigk	1850–55	Prague	..	..	4:1	9
Eppinger	1868–71	Prague	..	..	9:1	5
Berthold	1868–82	Berlin (Charite)	1:1	19:1	0.6:1	7.5
Schneider	1895–99	Munich	6.5:1	5.5:1	6:1	5.3
Wolowelsky	1895–1905	Basel	4.5:1	7:1	..	.
Kossinsky	1895–1910	Erlangen	3.4:1	9.8:1	2.4:1	8
Kirsch	1901–08	Munich	4.9:1	5.9:1	3.4:1	3.4
Scheel	1907–10	Copenhagen	3.5:1	75:1	2.9:1	20
Hart	1913–16	Berlin (Schöneberg)	1:1	2.1:1	1.2:1	1.6
Musa	1919–20	Berlin (Schöneberg)	0.8:1	2.5:1	0.6:1	2.7
Lehmann	1925	Vienna	1.7:1	2.6:1	1.2:1	1.3

in regard to open ulcers. If this trend continues, the autopsy ratio of two sites may eventually conform to the ratio of the clinical incidence.

Changes in the GU:DU ratio for the respective sexes follow the sa general pattern. The data are such as to shed no further light on the nat of the changes in the sex incidence of peptic ulcer.

Summary of the Present Status of Our Knowledge Concerning the Autopsy Incidence of Peptic Ulcer

As a preliminary to the ensuing discussion on the etiologic significa of the autopsy incidence of peptic ulcer, it is desirable to summarize conclusions which are justifiable from our analysis of the data.

The evidence does not permit a conclusion regarding whether the autopsy incidence of peptic ulcer has increased or decreased during the last 100 years. We interpret the data available as indicating that no significant change has occurred and that it has ranged from 5 to 10 per cent of the total population above 15 years of age in Western Europe and the United States.

Significant geographic and racial differences in the incidence of peptic ulcer almost certainly exist, but the extent and nature of these differences cannot as yet be clearly evaluated.

Ulcer of the Stomach

1. There has been no recognizable trend in the overall frequency of gastric ulcer. In the last 20 years, the incidence has varied from 2.8 to 14.8 per cent in various surveys.

2. There has been a decided decrease in the incidence of open gastric ulcers, and probably of scars in young females. In some places, a sex reversal in the incidence of gastric ulcer has occurred since 1910, so that slightly more males than females have gastric ulcer.

3. Chronic ulcer of the stomach is rarely found in individuals under 20 years of age. At autopsy, it is relatively most frequent from middle age (50 years) upward.

Ulcer of the Duodenum

1. There has been a progressive increase in the autopsy incidence of duodenal ulcer.

2. Duodenal ulcer is, and always has been, more frequent in men than in women; but the increase has affected both sexes proportionately, so that the sex ratio has remained generally consistent at approximately three to one.

3. At autopsy, the disease is relatively most common in the third and fourth decades of life.

Ratio of Gastric to Duodenal Ulcer

1. The GU:DU ratio has fallen progressively from approximately 7:1 to 1.2:1, though the ratio varies.

Discussion

Incidence of Peptic Ulcer

Geographic and Racial Differences. Kouwenaar's (143) report o the Eighth Congress of the Far Eastern Association of Tropical Medicine s of extraordinary interest and significance; his observations on the eopathology and ethnopathology of peptic ulcer open numerous avenues

of investigation which, if pursued systematically, should throw considerable light on the etiology of the disease.

Kouwenaar performed 3161 autopsies on inhabitants of Sumatra. The material consisted of 1370 Chinese men, 1269 Javanese men, 399 Javanese women, and 123 Tamils.* It is unfortunate that the last group constituted so small a segment of the autopsy population because it would be very important to know whether the incidence observed (4.9 per cent) is characteristic of this race. Presumably, more data will be forthcoming later; for the present discussion, this group, as well as the 399 Javanese women, will be omitted from consideration.

Thus we have left for comparison approximately equal groups of Chinese and Javanese males, almost all of whom were indentured laborers in the plantations of the East coast of Sumatra. All of the significant observations relating to these racial groups are presented, for convenience, in tabular form (Table 31). According to Bonne et al. (7), "absence of visible emotion is rather characteristic of the Malay race." But insofar as this may relate to the activity of the stomach, Brummelkamp (149) found that gastric acidity and motility in Malays was comparable to that in Europeans.

Bonne et al. (7) made extensive gross and histologic studies of the gastric mucous membrane in both Chinese and Javanese. No racial difference was apparent in the anatomic characteristics of the magenstrasse. Erosions and gastritis occurred in the stomachs of both races with equal frequency; therefore, the difference in the incidence of ulcers appears not to originate in a differing susceptibility to acute ulceration, but rather in the factors which cause erosions to progress to chronic ulcers. That secretory and motor disturbances are probably not important factors was apparent from the results of comparative studies of gastric secretion and motility in Chinese and Malays.

The opportunity for important studies in these two races which appear, superficially at least, to be exposed to almost identical conditions but in whom the incidence of peptic ulcer differs markedly is obvious. Among the points that require clarification is whether the Chinese men in the autopsy studies were recent immigrants, or at any rate, whether it is demonstrable that they had no ulcers before emigrating to Sumatra. We can find no autopsy statistics on the incidence of ulcer in Europeans residing in the Netherlands Indies; the clinical opinions on this matter are conflicting. Among the discussants of Dr. Kouwenaar's paper, a medical officer of the British naval base at Singapore stated that he had found gastric ulcer infrequently in either Chinese, Malays, or Indians, whereas

* A negroid group.

Table 31

COMPARISON OF INCIDENCE OF PEPTIC ULCER AND RELATED FACTORS IN CHINESE AND JAVANESE

	Chinese	*Javanese*
Number of Autopsies	1370	1269
Number of Ulcers and Scars	151	8
Incidence of Peptic Ulcer	11 per cent	0.6 per cent
Ratio of Gastric to Duodenal Ulcer	2:1	No breakdown for males; but of the 12 ulcers in both sexes, eight were duodenal, four gastric.
Occupation	Plantation laborers	Plantation laborers
Diet	A little more meat and a little more fat in the form of *lard*.	A little more fish; very little fat, usually in the form of *cocoanut oil;* more highly spiced foods.
Temperature of Food	Not stated	Not stated
Habits	Coffee and tobacco used equally by both groups; alcohol rarely; smoked opium, but author previously demonstrated that ulcers frequently existed before opium was started, and many Chinese started opium to control pain from ulcer; numerous ulcer patients never had smoked opium at all.	
Circulatory Changes (Local)	No differences found	
Autonomic Imbalance	More illnesses indicative of autonomic imbalance in Chinese, but seldom seen in either race; tend to react to tropical climate with irritative autonomic signs ("tropical neurasthenia").	Reduced irritability—opposite reaction to that of immigrants.
Emotional Tension	Evidence is contradictory	
Habitus	Insufficient evidence	
Other Factors: Burns, Enteric Infection, Traumata, Lordosis, Waistbinding, Focal Infection, Anemia, etc.	Not sufficient difference in the two races to account for the difference in incidence.	

it was common among Europeans stationed there; a physician who h practiced 13 years in Java said that he saw only two cases of clini gastric ulcer but encountered many gastric ulcer cases in European soldi who had been stationed in Java for a short period and not in those w had been there for a comparatively long time; Professor Snyders poin out that "the specialists on tropical diseases in Holland find high figu for gastric and duodenal ulcer among the patients who have resided fo long time in the Dutch Indies." Kouwenaar expressed the opinion t peptic ulcer was more prevalent among Europeans in the East coast Sumatra than in Europe, but de Langen (19) maintained that whe European suffering from peptic ulcer arrives in the Netherlands Indies, symptoms usually subside.

Clearly, until such time as careful observations are made, it will be possible, as Eagle and Gillman (25) concluded, to estimate the rela importance of such factors as diet, racial characteristics, and climat the etiology of peptic ulcer.*

* On the basis of clinical data, Dogra (146) believes that there is a difference in occurrence of duodenal ulcer between various religious groups residing in Mad South India. A breakdown of 51 cases of male duodenal ulcer patients operated u at the Government General Hospital yielded the following ratios:

Religion	*Ratio of Ulcer Cases to Total Male Population*
Hindus { Brahmins	1:32,868
Hindus { Non-Brahmins and depressed classes	1:5,017
Mohammedans	1:19,170

This would provide a remarkable opportunity to identify some specific etio factor if this tabulation represented the facts. However, these data are not consi with the subsequent report by the same author (147) that peptic ulcer in Travan Mysore, and Madura occurs with roughly the same frequency in all religious gr As a matter of fact, in his figures for Mysore, it appears that the incidence an Mohammedans is relatively greater than among Hindus, which is the reverse o situation shown above for Madras—unless most of the Hindu residents of Mysor Brahmins, in whom the disease is relatively infrequent. Dogra did not discuss points adequately in the publications referred to; however, in a subsequent p (148), he indicated that the etiologic aspects of his findings would be the subje another communication. It is anticipated that Dogra's further work on this subject be of great interest and value for the problem of peptic ulcer. One cannot help rem ing, though, that the difference between good autopsy data and even the most p taking clinical data is well illustrated by the difference between the reports of Ko naar and those of Dogra. The autopsy survey (Kouwenaar) leaves no doubt concer

AGE INCIDENCE. Peptic ulcer in pediatric practice is still enough of a novelty that a few cases comprise an unusual clinical report. Among the factors bearing on the etiology of peptic ulcer, the following are worthy of consideration in regard to the infrequency of the disease during childhood:

1. *Sex Hormones.* Sandweiss and his associates (102) summarized the evidence indicating a relationship between the sex hormones and peptic ulcer. Among other things, they showed that in 105 proven cases of peptic ulcer in children aged one to 12, the sex ratio was 1:1, as contrasted with an adult ratio (clinical data) of about five males to one female. This observation was considered to lend weight to the thesis that the female sex hormones in some way reduce the susceptibility to, or provide protection against, peptic ulcer (p. 317).

Only four of the autopsy reports reviewed permit a calculation of the sex incidence of ulcer exclusive of erosions in the first decade of life. Of

Table 32

Place	*Observer*	*Incidence of Peptic Ulcer up to Age 10*						*Ratio*
		Male			*Female*			
		No. Autop-sies	*No. Ulcers*	*Per Cent*	*No. Autop-sies*	*No. Ulcers*	*Per Cent*	
Erlangen....	Kossinsky	405	4	1.0	311	3	1.0	1:1
Mainz.....	Gruber & Kratzeisen	354	4	1.1	326	4	1.2	0.9:1
		759	8	1.06	637	7	1.1	1.06:1

hese four, Willigk (132) and Eppinger (26) reported no ulcers in this age roup. The data from the remaining two surveys (Table 32) appears to phold the contention of Sandweiss et al. that during the age period before :x hormone activity rises, the sex incidence of peptic ulcer is equal.

e marked difference in the incidence of peptic ulcer in two different racial groups ing under identical conditions. One can proceed with a program of investigation to the etiologic factors concerned in these differences, with complete satisfaction that e basic observation is correct. The same cannot be said for the clinical survey.

Similarly, Somervell (24) observed that while duodenal ulcer is generally very mmon in Travancore, the disease is practically unknown among the fishermen who e on the seacoast of this district and have a diet higher in protein. But no figures are esented.

2. *Gastric Secretion.* Insofar as the data in the literature permit a conclusion, the acidity in response to an Ewald-type test-meal does n reach the adult average level until sometime after the 15th year (12 (see p. 690). Whether, or to what extent, the acidity is altered in childr with peptic ulcer cannot be determined from the reports available, accor ing to Wolman (135).

3. *Dietary Excesses.* Childhood is generally a period of regular eati habits and abstinence from alcohol, tobacco, and coffee. Thus, childr are usually less apt than adults to be subject to the ill effects of such pra tices on the digestive tract.

4. *Psychosomatic Factors.* It is customary to assume that children are l burdened with anxieties and fears because they are ordinarily shelte and protected. However, it is more in accord with psychoanalytic conce to state that the psychic traumas suffered during the formative years repressed into the unconscious, and it is the resulting accumulation emotional "energy" which may later be discharged into the nerv pathways leading to the upper digestive tract. At any rate, the functio component of disease is perhaps less marked in children and is presuma absent from a psychosomatic aspect in the peptic ulcer of the newb (p. 643).

5. *Infection.* Considering the prevalence of contagious diseases, resp tory infections, and dental caries during childhood, the theory t systemic or focal infection plays a significant etiologic role in the devel ment of peptic ulcer is hardly tenable in view of the rarity of this dis in children. Although the gastric mucosa may be diffusely inflamed in course of febrile disease, ulceration hardly ever occurs, or if it does occu is not usually diagnosed.

The difference in average age between patients with duodenal u and those with gastric ulcer is but one of a number of differences rel to the location of the lesion. The factors involved are considered in discussion of pathologic physiology (Chapter 19).

Ulcer of the Stomach

Absence of a Recognizable Trend in the Incidence of Gas Ulcer. The fact that no discernible trend in the overall incidenc gastric ulcer is manifest in the autopsy statistics is not of course, a p that the disease is generally no more or no less prevalent now than it been in the past. So many opposing factors have influenced the data make it impossible to determine the true direction of the incidence. An these factors are:

1. Factors contributing to a decrease in the incidence: (A) Ma decrease in the number of gastric ulcers in females, and (B) better di

entiation of specific from peptic ulcer, or decreased incidence of specific ulcers.

2. Factors contributing to an increased incidence: (A) Moderate increase in the number of gastric ulcers in males, (B) better recognition of scars, and (C) greater percentage of people living to old age.

3. Other factors: (A) Lack of periodic autopsy surveys from the same institution.

Change in the Sex Ratio of Gastric Ulcer. The higher incidence of gastric ulcer in women prior to the present century has generally been attributed to one or more of the following three factors: (a) emotional tension, (b) chlorosis, and (c) tight lacing.

Emotional Tension. Chambers (13) doubted that any inherent biologic differences could be invoked to explain the greater susceptibility of females to this disease. He wrote:

> I should prefer attributing it to some of the habits of half civilized life which females, voluntarily or involuntarily, persist in; such as wearing ill-fitting stays, with rigid beams in front pressing upon the viscera; leaning forward to work immediately after food; swallowing their meals unmasticated; keeping decayed teeth in their heads; allowing mental emotion to check digestion; and a variety of other well known causes of the difficulties into which their stomachs fall.

LeNoir and Agasse-Lafont (67) found support for this view in their observation that the incidence of ulcer was higher among women in the earlier decades of life. These authors argued that it is almost always in the first part of her life that a woman "commits the most obvious errors of alimentary hygiene," whereas later she falls into the sheltered routine of a housewife. The disease comes to predominate among males in the middle years because it is then that men begin to suffer the effects of business responsibilities and dietary excesses. As Kimball (57) puts it, " . . . they live for the most part in a manner which puts all their organs on the rack."

Tidy (123) is of the opinion that "psychological influences" were not an important factor in the frequency of the disease in girls and young women. He noted that during the recent war the percentage of perforations among civilians in England was far higher in males; therefore, "psychological influences" act only as exciting stimuli superimposed on underlying factors which now affect mostly males, whereas in the Victorian age the predisposing factors especially affected young females. Mittelmann and Wolff (70) go a step farther; they consider the psychologic forces as fundamental to the etiology. They explain the sex reversal on the basis of change in women's social position in relation to men. Formerly, women could gain prestige only by marriage, and if a woman was not married by the time she was 27 years old, her position became a very trying one.

But during the period of striving and competition for "a man," ove emotional expression of the competitive effort was denied by soci custom; consequently, women were subjected to inner conflicts. The conflicts, according to the psychogenic theory, led to gastric ulcer. A ma on the other hand, while expected to be "master" in his household, cou nevertheless be emotionally dependent on his wife. Nowadays, the situ tion is reversed in that women are allowed free emotional expression ev though the problems which confront them leave them "frustrated, d satisfied, fault-finding and resentful." Men, however, may not lean f emotional support on their women; moreover, if the men are dissatisfi and resentful, there are no colonies to run off to, or frontiers to expan i.e., they cannot get away, as of yore, from the problems which oppr them. And finally, men are increasingly thwarted by the trend to i dustrialization, which more and more impersonalizes the individual.

Such is the explanation advanced by Mittelmann and Wolff, at least nearly as we can understand and summarize their view. It is doubt that all of these social changes took place, or exerted their effects on pep ulcer, completely and suddenly, for according to the authors, "perfo tions in young women increased rapidly in the beginning of the 19 century and died out completely and suddenly at the beginning of t 20th," and "uncomplicated ulcers probably fall into the same category perforated ulcers."

Chlorosis. The relationship of chlorosis to gastric ulcer was reviewed Riegel (94) and more recently by Redwitz and Fuss (93) in regard to t two salient facts bearing on this problem; viz., whether the anem preceded or followed the onset of ulcer symptoms, and whether chlor was accompanied by hyperchlorhydria. Redwitz and Fuss (93) conclud that the evidence did not support a significant etiologic role for chlor and anemia. We suspect that since the three entities—chlorosis, anem and acute gastric ulcer—tended to occur together and also disappear from the medical literature at about the same time, they were probal due to a common cause, which is discussed next.

Tight Lacing. In 1887, Rasmussen (91) described as a frequent autop finding a groove running across the anterior surface of the stomach. T groove, usually starting at the middle of the lesser curvature and coursi downward toward the greater curvature, where a marked indentation w found, corresponded to the line of pressure of the left rib margin. By far t greater number of mucosal scars occurred in this area. In fact, Rasmus stated that during a three month period when special attention was paid this phenomenon, in every instance of scar the presence of such a gro could be demonstrated. He construed these findings as explaining: (1) w scars often occurred symmetrically on opposite sides of the lesser curvatu

(2) why the lesions occurred in the middle of the lesser curvature; and (3) why the disease was more frequent in women, in view of the compression resulting from tight lacing. Schütz (111) and Schwarz (112) produced x-ray evidence to show that lesser curvature ulcers were situated at the point of maximum narrowing of the waist. So impressed was Schütz (111) with the consistency of this observation that he concluded his discussion on the prevention of gastric ulcer with the statement: "Above all must be sounded the watchword: 'Off with the corsets.' "

Bouveret (8) agreed that the corset was a "very fatal instrument for the stomach" but did not consider it responsible for many gastric ulcers. However, Redwitz and Fuss (93) grant that chronic compression may play at least a contributory role. Hansen (42) noted that the decreasing incidence of the lesion in females followed the decline of the fashion of wearing tight corsets. The author questions whether, by the same token, the adoption of belts instead of braces might not be partly responsible for the increasing frequency of juxtapyloric and duodenal ulcers in men.*

As a matter of fact, a rather good case can be made for abandonment of tight lacing as an explanation of the reversal of the sex incidence of gastric ulcer, as the following observations indicate.

1. One of the striking features of the older autopsy surveys is the greater ulcer:scar ratio in males. In other words, the number of healed lesions in relation to the number of open ulcers was uniformly greater among women (Table 24); moreover, a multiplicity of scars was a common finding in women. There are two explanations for these findings: (a) First, women were more susceptible to the disease but manifested a greater healing tendency. This time-honored pronouncement is no longer tenable for two reasons: first, a sex difference in susceptibility would have to be based on inherent biologic differences, and there is no evidence that the inherent differences have changed in the past 70 years. Second, the healing tendency in digestive tract mucosal lesions varies inversely with the susceptibility to ulceration. So, if the stomachs of women tended to ulcerate more easily, they would tend to heal more slowly. (b) Ulcers in women were brought on by compression of either the stomach walls or the larger gastric vessels, or both, by tight lacing; when the source of the compression was removed for a sufficient time for the ulcer to heal, a scar was left. Now, it stands to reason that if a woman developed symptoms of gastric ulcer and consulted a physician, she was put to bed—without her corset, in all probability—as a part of the treatment. Or, if she became pregnant, she had to relinquish her stays in the natural course of events,

* Einhorn (182) had the impression that ulcer symptoms were controlled more readily and recurred less often in patients wearing suspenders than in those wearing belts.

although in this circumstance the pregnancy itself would also have a salutary effect on the ulcer.

The above view is further supported by the high incidence of multiple scars, i.e., it points to a repetition of the sequence of events.

2. The gastric ulcers occurred principally at the age when women were most active socially and hence found it necessary to tolerate the tight lacing more frequently and for longer periods of time. Thus, Hansen (42) found that among males, the age distribution of ulcer cases has not changed, whereas among females the number of *young* cases has decreased considerably.

3. The ulcers were generally of the acute or subacute type, such as would be expected to be present if the ulceration resulted from external compression, the compression being removed when the lesion was sufficiently developed to cause symptoms. Of course, if the wearing of the corset were persisted in despite the symptoms, the ulcer would go on to chronicity, but it is not likely that such a practice was the rule.

4. The reported sex difference in the location of gastric lesions is very suggestive. In Lehmann's (66) autopsy material in Vienna, 75 per cent were women over 50 years of age, so that they passed their adolescence and young womanhood before the turn of the century. In this group there were 87 scars and only eight ulcers. Of the 87 scars, only two were in the pyloric region, the rest being in the proximal third of the stomach. This would correspond with the area of greatest compression. This is further supported by Hansen's (42) figures for the incidence of ulcer according to sites in the two sexes:*

Table 33

HANSEN'S DATA ON THE INCIDENCE OF ULCER IN MALES AND FEMALES DURING TWO DECADES, SHOWING A SHARP DECREASE IN ULCERS OF THE BODY OF THE STOMACH IN FEMALES

Sex	*Period*	*Site of Ulcers + Scars*		
		Body of Stomach	*Juxtapyloric*	*Total Gastric*
Male.....	1907–16	2.5%	1.2%	3.7%
	1927–36	2.5%	1.8%	4.3%
Female.....	1907–16	10.1%	0.6%	10.7%
	1927–36	3.4%	0.8%	4.2%

The most striking point in these data is the marked decrease in lesions of the body of the stomach in females, and it is obvious that this is the principal, if not the only, change which accounts for the reversing sex

* Recalculated from Hansen's (42) data.

cidence in this survey. That the reversal is not so much attributable the ulcer moving down around the pylorus is evident from the unanging frequency of (1) ulcers of the body of the stomach in males and) ulcers of the antrum in females.

5. The reported autopsy incidence of gastric ulcer was greater among ales in Chinese residents of the Netherlands Indies, and equal or greater Japan where tight lacing was not practiced; in Javanese natives, there as no sex difference in the incidence. Moreover, it appears in Table 24 at Japan was also the only country in which scars were relatively less mmon among women.

6. As to whether chronic compression of the stomach can predispose ulcer formation, Hansen (42) presented the following figures: Among ,335 autopsies, there were 102 (0.71 per cent) cases of kyphoscoliosis; nong 978 cases of gastroduodenal ulcer and scar, there were 17 (1.74 per nt) cases of scoliosis. Stated in another way, the incidence of peptic ulcer the general autopsy population was 6.8 per cent, while in kypholiosis it was 16.7 per cent.

To summarize, the evidence bearing on the sex reversal in the incince of gastric ulcer is such as to implicate the removal of some external tor as responsible for the formerly high incidence of this disease in men (167). *We are inclined to agree with those who have proposed that the wear- of tight corsets was the specific factor concerned in the development of at least one f of the gastric ulcers in women during the time when such corsets were in vogue.* If this be so, it follows that gastric ulcer has always been basically as ich a male as female disease—and perhaps more of a male disease, just has duodenal ulcer. This concept simplifies the problem of etiology to extent that it accords more significance to those investigations which k to explain the greater susceptibility of males on the basis of a sex ference in biologic structure or function. At least in the absence of tight ing, males have gastric ulcer as frequently as females.

Duodenal Ulcer

Increasing Incidence. The possible factors related to this increase y be summarized as follows:

1. *Greater Consumption of Alcohol, Tobacco, and Caffeine-containing Beverages.* considering this factor, we are hampered by some uncertainty as to ether the rising frequency of duodenal ulcer has involved both sexes. concluded from the data in Table 26 that it has, but Hansen (42) ld find no evidence in his survey that such is the case. He maintains t tobacco cannot be a factor because more women are smoking cigaes than ever before, yet the incidence in that sex has been unaffected. same argument could apply to the use of alcohol and the excessive

consumption of coffee. But there is an element of speciousness in this argument, because it may well be that these substances tax the mucosal resistance of *susceptible* individuals, among whom it seems that males predominate. In other words, even though we may admit that smoking has not increased the incidence of duodenal ulcer in women, we cannot conclude that smoking has in no way contributed to the increase of the disease in males.

2. *Psychogenic Factors.* An increased hospital admission rate for duodenal ulcer or its complications during a crisis such as war is sometimes cited as evidence that emotional tension can cause duodenal ulcer. *The evidence would be more convincing if someone were to prove that such increase consists substantially of new cases.* Dunn (150), in his review of the importance of gastroduodenal disorders in wartime, concluded that "the greater number of cases of dyspepsia in England must be related to emotional factors growing out of the war situation." Regarding the high incidence of peptic ulcer among military personnel, he mentions "the prolonged tension present in men who are mobilized for war but who have little opportunity to carry off their emotions in combatant activity," and in this connection he quotes Schindler's (151) opinion that "gastroduodenal ulcer will be a common disease in the United States Army." What Schindler said was " . . . since it is a frequent disease of the younger population it must necessarily be a frequent disease among draftees and soldiers." Likewise Nicol (168) stated that in the British Forces the incidence corresponded with what was to be expected from the civilian prewar figures.

It is generally agreed among American (152–155), Canadian (156, 157), and British (158–165) observers that only a relatively small percentage of cases of duodenal ulcer had their onset after induction into the armed forces. However, in most instances, the evidence of a pre-existing ulcer was based on prior symptoms, not on x-ray proof.*

Opinion on the importance of psychogenic factors in the onset or recurrence of peptic ulcer among military personnel was divided. Some (71, 152, 164) regarded anxiety as the paramount factor; some (156, 166) considered it an important but not a predominating factor, while others (161–163) did not believe it played any significant role. Flood (155) observed that healing time was delayed in a considerable proportion of the cases treated in a military hospital as contrasted with experience in civilian practice. The prolonged healing period occurred in those who appeared to be under strain, whereas those with relatively stable per-

* The evidence is further weakened by the probability that in many cases where military personnel were hospitalized for peptic ulcer, a special effort was made to elicit a history of symptoms which would make it possible to designate the ailment as EPTS (existing prior to service).

ality did well. In Zetzel's (153) experience, healing of the ulcer was id in patients who knew they were to be discharged; but when, as a ult of a change in medical policy, the diagnosis of peptic ulcer no longer ured automatic separation from the service, it was observed that healing not occur uniformly. Thus, there are good indications that psycho- ic factors may contribute to the chronicity of peptic ulcer.

It will probably be some time before we can formulate a clear picture the effect of wartime conditions on the incidence of peptic ulcer in the ilian population. There is little doubt that the incidence of perforations England rose sharply during the period of air raids (167, 169) but in h circumstances one must take account, in addition to emotional ss, of such factors as exposure, fatigue, and prolonged hunger. Tidy 7) was of the opinion that "psychoneurotic stimuli may pull the trigger, some other hand has previously loaded the gun." Moreover, a sudden rked increase in perforations was also noted in Scotland (170) and Swe- (171), where air raids did not occur. It remains unsettled whether, o what degree, an increase in perforations indicates an increase in new es of peptic ulcer. Odom and De Bakey (173), in this country, noted t from 1929 to 1938, a period of economic stress, the percentage of pital admissions that were ulcer cases rose 1.5 times, while the rate of te perforations increased seven-fold. In this instance, the observed foration rate was not representative of the observed ulcer rate, but it s not rule out the possibility that the incidence of ulcer actually rose *passu* with the perforations, because the acute perforations were almost ain of being admitted to the hospital while the uncomplicated ulcers e not. Petren (171) regarded it as "highly probable or virtually ain that such a marked increase—some 35 per cent—in the frequency erforations indicates a significant increase in the frequency of ulcer" that his findings support "the impression of many Swedish internists peptic ulcer has increased in Sweden during the last two years of war crisis (1942–43), especially 1942." Among those who entertained the ical impression of a rising incidence was Sällström (172) who, however, d not substantiate this impression when he investigated the matter. found that the number of ulcer cases seen in the clinic did not change erially, but that the number admitted to the hospital rose significantly. s he attributed to the difficulty of obtaining a proper diet at home due ationing of food. And even under treatment in the hospital, healing protracted, which may have been a reflection of the changes in tment necessitated by food shortages. During the war years, the ulcer s provided in the hospital were lower in caloric value, proportion of and vitamin content than had previously been available.

n the aftermath of war, the fear and insecurity resulting from depriva-

tion, particularly of food, might serve as a test situation for the stud importance of psychogenic factors; but concomitant physiologic turbances such as result from prolonged hunger would have to be ru out.*

Ehrmann (5) states, without supplying any figures, that observa based on 15,000 autopsies showed that at the time of deficient nutrition Germany during World War I, there was a marked increase in incidence of peptic ulcer. This increase was ascribed principally to longed secretion on an empty stomach.

Whether people are nowadays under more profound inner stre than, for example, during the colonization of this country, neither we anyone else can say. Consequently, we cannot hazard an opinion whe the rising incidence of duodenal ulcer has been preceded, accompanie followed by increasing psychic maladjustments.

Predominance of Duodenal Ulcer in the Male Sex. Several fac have been postulated to explain why duodenal ulcer is so much m common in men than in women.

1. *Anatomic Differences in the Upper Digestive Tract.* Mayo (142) st that the first part of the duodenum in women is often transverse, as trasted with its usually ascending course in men. He considered the acid chyme from the stomach was therefore more easily neutra

* Hamperl (41) appears to be satisfied that a marked rise in the incidence of p ulcer occurred in certain parts of Russia during the years of famine consequent First World War. Valid autopsy statistics are lacking, but the number of cases ope upon in 1921 was 20 times that in 1914. The degree of malnutrition suffered b Russian people may be deduced from the following figures on the average daily intake of the residents of Leningrad:

Year	Calories	Year	Calories
1914	2800	1919	800
1917	1760	1920	790
1918	1500		

Hamperl (41) considered that in addition to the effects of the dietary deficiency the hunger state, the emotional factor was also to be regarded as contributing t sudden increase in the disease. Illustrative of the extent of this increase is the quot from a report by two Russian authors:

During the hunger years, the influx of ulcer patients from the remote areas state was so large (in the single year 1921, 630 ulcer patients alone went throu operating room) that a number of them were forced to await their turn for se Ulcer reached the proportions of a true epidemic. In the first crowded perio ulcer patients dragged along in their pitiful existence, spending the nights o benches of the out-patient clinic; in warm weather they formed a camp on the gr of the hospital. It was necessary to improvise, in the vicinity of the surgical divi separate shelter for ulcer patients, somewhat in the manner of a barracks, which referred to amongst us by the name "Ulcer Hotel," a designation which the pa patients themselves, in their grim humor, introduced.

upper duodenum in women. We find no mention, in text books on
gy, of a sex difference in the course of the duodenum,* and we are
belief that if such a structural difference exists it is of no functional
ance.

Gastric Secretion. Curves of gastric acidity show significantly higher
e values for males throughout all age groups (see p. 690). Whether
ference is sufficient to account, even in part, for the greater sus-
lity of males to duodenal ulcer is not known; though relatively
it should be considered a theoretic possibility.

Sex Hormones. Renewed interest has been shown in recent years in
tionship between endocrines and peptic ulcer; the observations of
iss et al. (102) and Winkelstein (133) have focussed attention
larly on the sex hormones. The present status of the investigations
his line has been reviewed (Chapter 13). There is good evidence
onset or recurrence of peptic ulcer in women is frequently affected
action of sex hormones, either directly or via the pituitary gland.

Psychosomatic Differences. Considering the general trend toward the
ipation" of women in present-day society, one would expect the
ex to share more and more in the diseases which are initiated or
ted by inner conflicts. Nevertheless, the incidence of duodenal
women has thus far shown no tendency to approach that in men.
ng to the views of Mittelmann and Wolff, this is explainable on
nds that women may freely express their emotions, whereas men
t.

Conclusions

r examining the literature and numerous hospital autopsy records,
come to the conclusion that a reasonably accurate figure for the
incidence of peptic ulcer cannot be obtained by going back over
records. It is because this is the only kind of data hitherto available
is compelled to speculate, rather than speak with assurance on
e incidence is or has been. We have concluded that duodenal ulcer
more common now than in bygone years, but even this is open to
t, and the argument hinges on the question whether or not the
reports of 30 years ago were reliable.

herefore conclude that an autopsy survey must be undertaken as a
study in order to provide reliable data concerning the incidence

red Jenner Hodges was consulted on this point. He says that if there is any
in the anatomic course of the duodenal cap in the two sexes, it is not suffi-
arked to commend itself to the attention of himself or his associates in many
of observations at the fluoroscopic screen.

A summary of what we consider to be the present status of our knowledge regarding the autopsy incidence of peptic ulcer is provided on page 480.

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OUTLINE OF CHAPTER 15

Anatomic Evidence Bearing on Pathogenesis

I. Sites of Predilection in Man
   A. GASTRIC ULCER
      1. Location of Chronic Gastric Ulcer
         a. Autopsy and Surgical Specimens
         b. Relation to the Incisura Angularis
            (1) Postmortem and Surgical Data
            (2) Roentgenologic Data
         c. Differences in Site of Predilection of Gastric Cancer
         d. Predilection for the Posterior Wall
         e. Tendency of Anterior Wall and Pyloric Ulcers to Per... and of Posterior Wall Ulcers to Hemorrhage
         f. Location of Acute Gastric Ulcer
         g. Location of Subacute Ulcer
   B. DUODENAL ULCER
      1. Location of "Chronic" Duodenal Ulcer
      2. Location of Acute and Subacute Duodenal Ulcer
   C. ANASTOMOTIC ULCER
      1. Location of Postoperative Jejunal and Gastrojejunal Ulc... "Anastomotic Ulcer"
         a. Terminology
         b. Relative Incidence of Gastrojejunal and Jejunal Ulcer
         c. Location of Anastomotic Ulcer
   D. PEPTIC ULCER IN THE COLON
   E. PEPTIC ULCER IN THE ESOPHAGUS
   F. PEPTIC ULCER RESULTING FROM HETEROTOPIC GA... MUCOSA
II. Factors Concerned in Determining the Sites of ... dilection
   A. THE LESSER CURVATURE
      1. Anatomy and Physiology
      2. Facto... of Intestinal Epithelium in the Mucosa of the ... Curvature
      3. Factor of Exposure to Irritant Drinks
      4. Factor of Exposure to Mechanical Injury
         a. Pressure from Outside the Stomach and Duodenum
         b. Pressure from Inside the Stomach

5. Factor of Relative Fixation of the Lesser Curvature
6. Factor of Motility of the Stomach
7. Factor of Mobility of the Gastric Mucosa on Underlying Structures
8. Significance of the Form of the Ulcer in the Lesser Curvature
9. The Phylogenetic Factor

B. DUODENAL BULB

C. POSTOPERATIVE JEJUNAL AND GASTROJEJUNAL ULCER

SITES OF PREDILECTION IN ANIMALS

A. LOCATION OF SPONTANEOUS ULCERS IN ANIMALS

B. LOCATION OF EXPERIMENTAL ULCERS IN ANIMALS

1. Selectivity of Ulcerogenic Procedures for the Stomach or Duodenum
2. Selectivity of Ulcerogenic Procedures for Regions Within the Stomach
3. Selectivity of Ulcerogenic Procedures for Regions Within the Duodenum and Jejunum

C. EXPLANATION OF THE LOCATION OF EXPERIMENTALLY INDUCED ULCER IN ANIMALS

D. REPAIR AND HEALING IN THE REGION OF THE LESSER CURVATURE

E. VASCULAR TUGGING AND OTHER FACTORS IN RELATION TO THE VULNERABILITY OF THE LESSER CURVATURE

F. COMMENT

OTHER ANATOMIC ITEMS

A. NUMBER OF PEPTIC ULCERS IN A SINGLE SPECIMEN

1. Number of Gastric Ulcers in the Same Stomach
2. Number of Ulcers in the Same Duodenum
3. Association of Acute and Chronic Ulcer
4. Association of Chronic Ulcer of the Stomach and of the Duodenum
5. Significance of the Discreteness of Peptic Ulcer

B. SIZE OF PEPTIC ULCERS

1. Size of Gastric Ulcers
2. Size of Duodenal Ulcers
3. Comment

C. FORM AND HISTOLOGIC CHARACTERISTICS OF A PEPTIC ULCER

D. RECURRENCE OF PEPTIC ULCER AT THE SITE OF A PREVIOUS SCAR

E. EXTENSION OF THE ULCER

1. Extension to the Serosa
2. Extension to Adjacent Organs
3. Adhesions

SUMMARY

CHAPTER 15

Anatomic Evidence Bearing on Pathogenesis

Sites of Predilection in Man

It is well known that peptic ulcer, whether located in the stom or duodenum, tends to occur in certain locations. These sites of predi tion will have to be explained before the pathogenesis is fully understoo

Gastric Ulcer

Location of Chronic Gastric Ulcer

Autopsy and Surgical Specimens. It has been well established th large majority of chronic gastric ulcers are located on or within one i of the lesser curvature. In Table 34, it is to be noted that 63 per cen

Table 34

Location and Site of Perforation in a Series of 200 Chronic Gastric U at Autopsy*

Location of Ulcer	*No. of Specimens*	*Number Perforated*			
		Anterior	*Posterior*	*Both*	*T*
1. Ulcer located entirely or mainly on the anterior wall. .	29	18 (62%)	0	0	18
2. Ulcer located entirely or mainly on the posterior wall. .	45	4 (9%)	4 (9%)		8
3. Ulcer located about equally on anterior and posterior wall of lesser curvature and pyloric canal	126 (63%)	37 (29%)	1 (1%)	4 (3%)	42
4. Totals	200	59 (29.5%)	5 (2.5%)	4 (2.0%)	68

* Hurst and Stewart (1).

† Of the 68 perforated ulcers, 59, or 85 per cent, perforated anteriorly.

tric ulcers observed at autopsy were located on the lesser curvature, Table 35, that 96 per cent in the surgical series and 82 per cent in topsy series were located on or within one inch of the lesser curva-

Table 35

OF CHRONIC GASTRIC ULCER IN 210 POSTMORTEM SPECIMENS AND 170 CLINICAL SPECIMENS*

	Autopsy Series		Clinical Series		Total	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
rvature†	172	82	164	96.5	336	88.4
anal	26	12	6	3.5	32	8.4
	2	1			2	0.5
wall	4	2			4	1.1
wall	6	3			6	1.6

rst and Stewart (1).
a includes one inch on either side of the lesser curvature, but excludes pyloric l cardia.

ewart explains the larger percentage of pyloric canal ulcers in the series (Table 35) than in the surgical series by pointing out that c canal ulcer is more likely to perforate and cause death and that d of this autopsy series had perforated. The data in Table 36 show

Table 36

STANCE BETWEEN ABORAL MARGIN OF THE CHRONIC ULCER AND THE PYLORIC RING (170 SURGICAL SPECIMENS)*

	No.	Per Cent	
loric canal† (1st inch)	6	3.5	
2 inches from pylorus	38	22.4	
3 inches from pylorus	58	34.1	63.5% / 85.9%
4 inches from pylorus	50	29.4	
re than 4 inches	18	10.6	

* Hurst and Stewart (1).
† Includes two cases in which the ulcer abutted on the pyloroduodenal junction.

er cent of the ulcers in the surgical specimens were located from ur inches proximal to the pyloric ring (1). In 125 cases of gastric postmortem, Wright-Smith (8) found 45 per cent located on or lesser curvature, one inch on either side of the incisura, and 45 per

cent located in the prepyloric region. Orator (9) observed similar grou ings, though fewer ulcers were located prepylorically.

The results of several compilations on the location of gastric ulcers a illustrated in Table 37 (2, 3). Though these are not as reliable as those

Table 37

POSITION OF CHRONIC GASTRIC ULCER (POSTMORTEM)

	Martin's Compilation (2)		*Hauser's Compilation (3*	
	No.	*Per Cent*	*No.*	*Per Ce*
Lesser curvature	726	35	587	41.5
Posterior wall	585	28 (77)	183	12.9
Pars pylorica (vestibule and canal)	291	14	359	25.5
Anterior wall	182	9	82	5.8
Cardia	134	6.5	78	5.5
Fundus	62	3.0	60	4.2
Greater curvature	75	3.6	64	4.5
Anterior and posterior wall (saddle)	14	0.67	..	..
Totals	2,069		1,413	

Stewart because they represent the reports of a number of observers, th show the same predilection of gastric ulcer for the lesser curvature. should be noted that the larger percentage of Stewart for the les curvature location is due to the fact that he included 2.5 cm. on each si of the lesser curvature in his definition.

RELATION TO THE INCISURA ANGULARIS: *Postmortem and Surgical D* Most gastric ulcers appear to be located in the region of the incis angularis and in the prepyloric region, though the literature is not cl on this point. *The autopsy data* of Portis and Jaffe (4) show that appro mately 60 per cent of gastric ulcers are located within 6 cm. proximal the pyloroduodenal junction. The same is true of those German auth who provide such information (3, 5). This agrees with the data fr surgical specimens of Hurst and Stewart (Table 34).

The correlation of the roentgenologic and anatomic angulus is certain. We can find no report on this subject. Nevertheless, in figure average longitudinal measurements of 155 stomachs at postmortem shown, the location of the incisura being based on the location of change from fundic to pyloric mucosa (6). Introducing Stewart's d (Table 34) from surgical specimens (empty stomach) into figure 95, found that 60 per cent of the ulcers are located in the same region as fo by Jaffe and Portis in autopsy specimens. Eusterman and Balfour (7) s

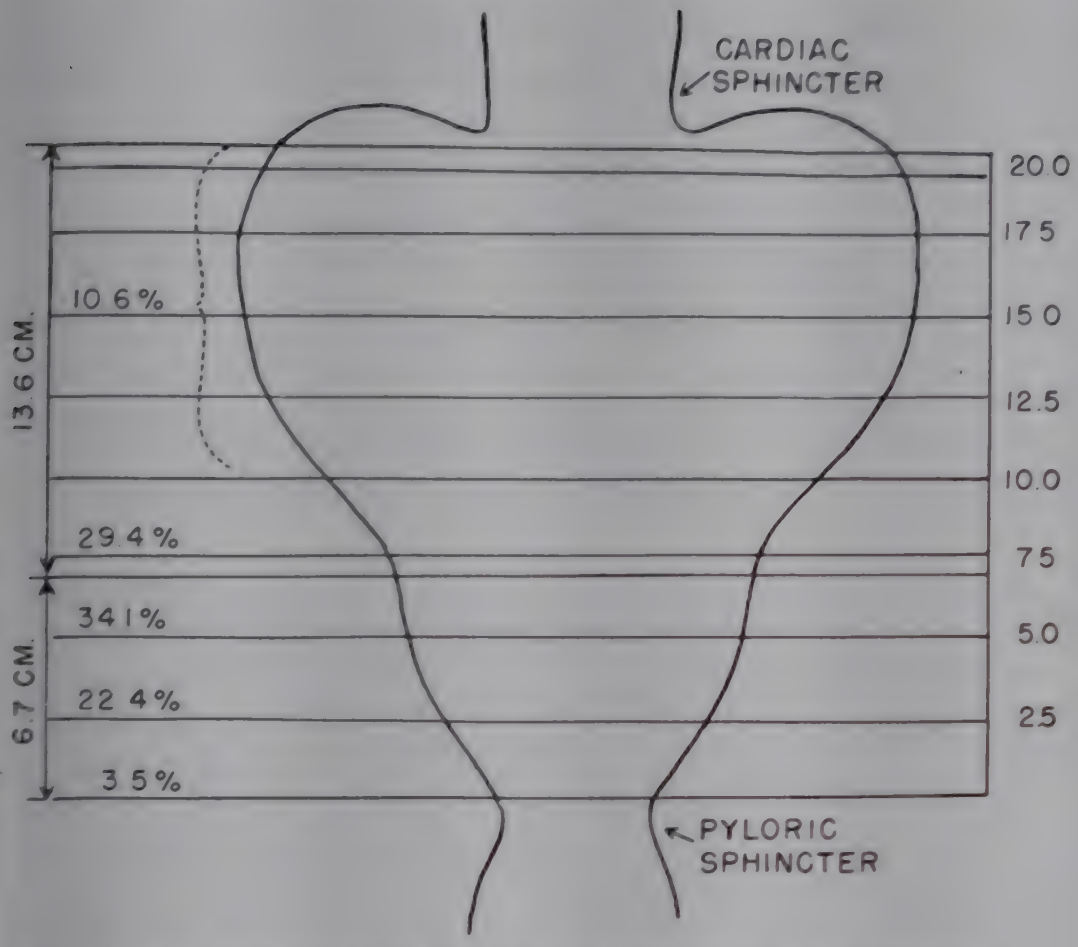


FIG. 95. The distribution of ulcers in various parts of the stomach.

of 617 gastric ulcers collected by them (source not given), 68 per cent located in the region of the incisura, chiefly proximal to it. A similar ment would apply to the data in figure 95.

oentgenologic Data. The roentgenologic data indicate that most ulcers cated at or proximal to the incisura angularis (9, 10, 11). Templeton

Table 38

SITE OF GASTRIC ULCER IN MEN AND WOMEN

Sex	Cardia		Mid-Lesser Curvature		Incisural Region		Canal and Pre-Pyloric		Other Location		Total	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
.....	8	3	16	7*	126	57	69	31*	4	2	223	100
n.....	6	5	25	20*	69	56	20	16*	3	3	123	100
l.....	14	4	41	12	195	56	89	26	7	2	346	100

ifference is statistically significant.

(12) states that the roentgenologist finds most gastric ulcers along th vertical portion of the lesser curvature, only occasionally along th horizontal portion, and rarely in the canal. Westphal (10), in a series 50 cases, found all but one of the craters proximal to the incisura. More conformity with the general impression, Ihre and Müller (13) found t craters concentrated, first, in the incisural region, and, second, in t prepyloric region. They found significantly more craters in the prepylor region of men than of women (Table 38) and more in the mid-less curvature region of women.

The data in Table 39 show how information on the location of t crater as located by the roentgenologist and pathologist vary.

Table 39

SHOWING LOCATION OF CRATERS IN THE STOMACH AS OBSERVED BY X-RAY AND POSTMORTEM*

Location	*Ihre & Müller X-ray 346 Cases Per Cent*	*Henänen X-ray 182 Cases Per Cent*	*Stewart Postmortem 210 Cases Per Cent*	*Madelung Postmorten 1246 Case Per Cent*
Lesser curvature region	..	..	82	..
Corpus	12	35.5	..	28.1
Angulus	56	13.7	..	33.8
Pyloric canal	26	33.0	12	22.5
Cardia	4	9.3	1	..
Ant. wall	..	..	2	8.4
Post. wall	..	..	3	6.6
Great. curvature	..	..	..	0.8
Other sites	2	8.5	..	..

* From Ihre and Müller (13).

It must be kept in mind that the roentgenologist works with a partia filled stomach and the surgeon and pathologist with an empty stomach a rule. We do not know whether the incisura of the pathologist is the sa as that of the roentgenologist. Information on this point is needed to br into harmony the roentgenologic and pathologic data. However, gast ulcer appears to concentrate, first, about the incisura and just proximal it in both men and women and, second, in the prepyloric region, chie in men, and the mid-region of the vertical portion of the lesser curvatu chiefly in women.

DIFFERENCES IN SITE OF PREDILECTION OF GASTRIC CANCER. The diff ence in the site of predilection of gastric ulcer and gastric cancer is interest in relation to the etiology of the two conditions. Whereas gast

r occurs chiefly in relation to the lesser curvature, gastric cancer irs chiefly in relation to the prepyloric region. In a compilation of 500 cases by Welch and 234 cases by Mathieu (see Ewing (14)), roximately 60 per cent of the gastric cancers started in the prepyloric on. The more recent postmortem data of Stewart are shown in Table here 66 per cent of 106 cancers originated in the prepyloric region. e also refs. 7, 15.)

Table 40

TION OF CHRONIC ULCER, ULCER-CANCER, AND PRIMARY CANCER IN A SERIES OF 358 OPERATION SPECIMENS AND 374 POSTMORTEM*

Site of Lesion	*Surgical*			*Postmortem*	
	Chronic Ulcer	*Ulcer-Cancer*	*Primary Cancer*	*Chronic Ulcer*	*Cancer*
oric canal (1st inch) . .	15 (5.7%)	5 (29%)	71 (84.5%)	26 (12%)	109 (66.5%)
ser curvature region . .	248 (94.3%)	12 (71%)	9 (10.7%)	172 (82%)	21 (12.8%)
st of stomach	. .	. .	4 (4.8%)	12 (6%)	34 (20.7%)
Total†	263	17	84	210	164

* Hurst and Stewart.

† In three cases, two chronic ulcers co-existed, and in three others, there were dependent ulcers and cancers.

PREDILECTION FOR THE POSTERIOR WALL. The predilection for the posterior wall as compared to the anterior wall of the stomach is indicated by the data in Table 34 and Table 41. This has received much attention

Table 41

LOCATION OF DUODENAL ULCERS (POSTMORTEM)*

Location	*Open and Healed Ulcers*	*Open Ulcers Only*	*Open Chronic Ulcers of Duodenum*		
			No. Seen	*No. Perforated*	*Per Cent Perforated*
nterior wall	64	77	104	73	70
osterior wall	62	49	76	10	13
oth walls†	104 (45%)	27 (17%)	. .	. .	. .
Total	230	153	180	83	46

* Hurst and Stewart (1).

† Sometimes called "Kissing Ulcers."

because of the greater tendency of anterior wall ulcers to perforate (Tables 34 and 41). The ratio of anterior to posterior wall perforations varies in different reports as follows: Hurst and Stewart, 7:1 (1); Moynihan, 7.5:1 (16); Paterson, 6.5:1 (17); Hawkins and Nitch, 3.9:1 (18).

Tendency of Anterior Wall and Pyloric Ulcers to Perforate and of Posterior Wall Ulcers to Hemorrhage. Stewart (1) makes the interesting observation that *ulcers in the pyloric and prepyloric region are most likely to perforate.* In an autopsy series of 119 ulcers, 65 were within two inches of the pyloric orifice, and 54 were above on the lesser curvature. Among those near the pylorus, 29 (45 per cent) had perforated, whereas only 12 (22 per cent) of those above were perforated.

Fatal hemorrhage is more likely to occur from an ulcer of the lesser curvature or posterior wall of both stomach and duodenum (1, 2). Fatal hemorrhage occurs so infrequently that reliable statistics are not available.

Location of Acute Gastric Ulcer. Acute ulcers of the stomach are generally multiple and irregularly distributed. They occur more frequently in the distal half of the stomach. Aschoff (19) differentiates between two types of acute ulcers as regards location and size. One type consists of very numerous anemic or hemorrhagic erosions which occur chiefly in the fundus and are sometimes referred to as the "stigmata of Beneke." These are believed to result from vascular spasm or injury (p. 180). The second type consists primarily of less numerous erosions of the longitudinal rugae in the region of the lesser curvature.

Location of Subacute Ulcer. This ulcer, which has a slightly indurated margin due to edema and some fibroblastic proliferation, is not commonly seen in man. Stewart (1) in 4,000 autopsies placed only 14 cases of ulcer in this category. Most were located in the region of the lesser curvature.

Duodenal Ulcer

Location of "Chronic" Duodenal Ulcer

The location of duodenal ulcer, like that of gastric ulcer, is such that in opening the stomach, the incision along the greater curvature can be extended and continued along the mesenteric border (concavity) of the duodenum without damaging a duodenal ulcer which may be present. This is because a duodenal ulcer is located on the anterior or posterior wall, or both, except in rare instances.

All observers agree that 95 per cent of duodenal ulcers are located within the first 3 cm. of the duodenum. Most are located from 5 to 20 mm. distal to the pyloric orifice. It is uncommon for an ulcer to extend across the mucosa of the pyloric orifice from either direction (Ulcer-en-cheval of Collin). It is also uncommon for an ulcer to be found as distal as the papilla of the common bile duct (20).

We interpret the literature as indicating that duodenal ulcer is located as frequently on the anterior as the posterior wall when open ulcers and scars combined are considered. Some report a greater incidence of open ulcers on the anterior wall (Table 41) (16, 20, 23–25). Others report a greater incidence on the posterior wall (26, 27). The differences are sometimes not statistically significant; for example, Clairmont (29) in Switzerland found 73 ulcers on the posterior and 60 on the anterior wall of the duodenum, a difference which is probably due to chance or random sampling. Again, the difference may be due to the selection of cases. Anterior wall ulcers are more frequently seen by surgeons because they perforate more frequently and would be seen in hospitals which specialize in gastric surgery. The posterior wall ulcer, which is said to bleed severely, does not come to autopsy so frequently as perforated ulcer.

Location of Acute and Subacute Duodenal Ulcer

Acute ulcers of the duodenum are irregularly distributed and may be seen in the second and third portions where chronic duodenal ulcer is rarely seen.

It is doubtful whether *subacute* ulcers of the duodenum can be differentiated with any certainty. It might be pointed out that Nicolaysen (30) and Melchior (31) have suggested that what is called a chronic duodenal ulcer is in reality a continuous series of subacute or acute ulcers. This is supported by the relative rate of healing of gastric and duodenal ulcers (p. 150).

Anastomotic Ulcer

Location of Postoperative Jejunal and Gastrojejunal Ulcer, or "Anastomotic Ulcer"

Following gastrojejunostomy, peptic ulcers occur at and away from the line of anastomosis. When the ulcer breaches the line of anastomosis, it is called a *marginal ulcer* or a *gastrojejunal ulcer*. In such an ulcer, it is uncommon for much of the gastric mucosa to be involved. When there is a band of jejunal mucosa between the ulcer and anastomotic line, the ulcer is called a *jejunal ulcer*.

Terminology. The terminology is frequently confused by the author of an article on this subject, sometimes because the exact location was uncertain and sometimes because the author believes a true marginal ulcer does not occur. For example, Eusterman and Balfour (7) believe that all ulcers after gastroenterostomy start in the jejunum and extend to the anastomotic line and occasionally into the gastric mucosa. We agree with this opinion if the anastomosis is carefully made. (We very rarely see a marginal ulcer in the Mann-Williamson dogs we prepare. We believe this is due to good tailoring of the anastomosis. The ulcers have been uniformly

observed to start away from the anastomosis.) Nevertheless, a c distinction should be made between the two sites, since the etiology o two may prove to be different in part. If this is so, a more approp operative procedure may markedly reduce the incidence of mar ulcer.

Relative Incidence of Gastrojejunal and Jejunal Ulcer. literature on the relative incidence of gastrojejunal and jejunal ulc meager. Of 129 cases collected by Wright (32), 62 were jejunal an gastrojejunal. In 43 cases collected by Birgfeld (35), the ulcer was ga jejunal in 22 cases. In 22 cases, Stewart (1) found 12 jejunal an gastrojejunal. The finding of more gastrojejunal than jejunal ulce characteristic of the older literature. For example, prior to 1932 Starli (34) collected 2500 cases of anastomotic ulcer in which 75 per cent gastrojejunal and 25 per cent jejunal. In 512 cases (corrected from observed at the Mayo Clinic (36), only 56 per cent involved the a tomotic line. Still others (37, 38) report that the anastomotic ulcer oc most commonly opposite the stoma nearer the insertion of the mesen In Wright's (32) cases, the location of the ulcer appears to depen whether an anterior or posterior gastroenterostomy is made. In 72 c of an anterior anastomosis, 43 of the ulcers were jejunal and 31 ga jejunal, and in 59 cases of posterior anastomosis 28 were jejunal 31 gastrojejunal. This, however, is a difference which could occu chance. We interpret the data available as indicating that anastom ulcer in man is as frequently jejunal as gastrojejunal.

Location of Anastomotic Ulcer. The anastomotic ulcer most c monly occurs on the anterior wall of the jejunum, whether it is locate or away from the anastomotic line (5). The data in the literature, howe are not presented so as to permit one to determine whether the ant location is true of both a posterior and an anterior anastomosis.

All are agreed that the ulcer is rarely located in the jejunum n than 3 cm. away from the stoma, although ulcers have been describe far away as 10 cm. and 30 cm. (5). It is more commonly located in efferent loop than the afferent loop when it is away from the stoma. example, in 120 reported perforations collected from the literature Toland and Thompson (39), the site was recorded in 96 cases. It was in jejunum in 74 cases (efferent limb, 45; opposite stoma, 19; afferent li 10), in the anastomotic line in 19, and in the stomach in three.

Peptic Ulcer in the Colon

A jejunal ulcer may perforate into the colon and acid chyme enter the colon. In such instances, a peptic ulcer of the colon may oc (1) (42).

Peptic Ulcer in the Esophagus

Chronic peptic ulcers of the esophagus, as evidenced by open ulcers nd scars, occur in the lower third of the esophagus almost entirely in the st 3 cm. (44). Acute ulcers have the same location. Chronic and acute cers may extend into the stomach and are really gastroesophageal ulcers. ccording to Jackson (43), these ulcers never appear in the presence of halasia of the cardiac sphincter or cardiospasm, in which condition the ntents of the esophagus are generally alkaline.

Peptic Ulcer Resulting from Heterotopic Gastric Mucosa

Heterotopic gastric mucosa containing oxyntic or parietal cells may pear in the esophagus or any portion of the small intestine (45). It is ost commonly located in Meckel's diverticulum, which occurs in 2 per nt of persons. In some cases, there is a sufficient development of gastric ucosa of the acid secreting type that an ulcer occurs in the diverticulum r in the ileum into which the diverticulum drains (5, 47).

Factors Concerned in Determining the Sites of Predilection

The factors concerned in determining the sites of predilection are nportant from the standpoint of the pathogenesis of peptic ulcer. This pic has received such extensive discussion in the literature that only the ajor articles will be referred to.

The Lesser Curvature

Anatomy and Physiology. The lesser curvature of the human stomach s thought to be homologus to the "esophageal groove" or "canalis astricus" of ruminants. The musculature of the fore-pouched stomach f ruminants is so arranged that fluid may pass from the esophagus to the yloric pouch (abomasum) without entering the three pouches that open nto the canal (48). In man, monkey, dog, and cat, the oblique muscula- ure, the inner layer of the muscularis propria, is so arranged that its ontraction could shorten the lesser curvature and decrease the angulation t the incisura. When the stomach of these species is opened along the greater curvature and the organ is flattened out with the mucosa upper- most, it becomes quite evident that the mucosa and muscularis mucosa f the entire lesser curvature is fashioned into a structure sometimes referred as a "groove" or "magenstrasse." The groove descends from the cardiac zone to the pyloric canal and is set off from the rest of the stomach by two to four longitudinal folds of mucosa. *The mucosa* of the groove is not so freely movable upon the muscular coat (49). According to Billenkamp,

the epithelium is not so thick as that of the rest of the stomach and t transition from acid secreting (fundic) to mucus secreting (pyloric) glar occurs relatively high in man. The *blood supply* to the lesser curvature, t pyloric part of the stomach, and the duodenal bulb is stated to be l abundant and to have fewer anastomoses between the arteries than in t rest of the stomach (50–54, 56–59). Cole (55) has suggested that the lov branches of the left gastric artery are subject to considerable tension wh the individual is in an upright position, particularly in a person of t habitus asthenicus or with a long, J-shaped stomach. We believe that would be advisable to study the blood supply of the stomach more than has been. It is quite possible that in the evolutionary development o fundic mucosa for the secretion of acid of high concentration, wh requires a copious blood flow, a similar increase in blood flow for adequ protection was not provided to the lesser curvature, pyloric antrum, a the duodenal bulb.

Nerves. Schabadasch (60) has performed studies on the distribut of the myenteric plexus of the cats' stomach. The prepyloric and pylo regions of the plexus appeared to receive more vagal fibers per unit surface than the fundus. The density of the plexus is greater at the les than at the greater curvature. The ganglionic nodes of the myente plexus are larger in the pyloric region and lesser curvature than in ot portions of the stomach. Brandt (61) found the greatest number ganglionic cells in the myenteric plexus in the lesser curvature.

Secretion. Alley (62) and Davidov (63) have studied the gastric secret of pouches made from the lesser curvature. They reported that this regi in comparison with the usual Pavlov type of greater curvature pouch, more under the influence of the vagus nerves and gave less mar response to secretagogues and histamine. The data submitted suggest do not establish such a conclusion.

Motility. Klein (64) observed that the mucosa of the lesser curvatur more sensitive to mechanical stimuli than other regions of the stoma Irritation may induce an hourglass contraction. Most of the more vigor waves of contraction, especially early in digestion, start in the region of incisura angularis. The lesser curvature being shorter than the greater, waves of contraction persist relatively longer at any particular place the lesser than on the greater curvature. This is so evident sometimes at incisura that the wave of contraction appears to stop progressing an referred to as a "standing wave."

Factor of Intestinal Epithelium in the Mucosa of the Les Curvature. Some have suggested that ulcers occur in the lesser curva region because congenital heterotopic islands of intestinal epithelium found there (65–68). Chuma (65) was never able to demonstrate th

tches of intestinal elements in the stomach of the newborn infant or in ildren. Of 59 adults, 15 had such patches, but these were always asso- ted with frank gastric disease such as gastric ulcer or carcinoma. So, he ncluded that these patches of intestinal epithelium were the result, not e cause, of pathologic processes and arise from regeneration of eroded eas or perhaps metaplasia. In fact, Askanazy (69) and Gruber (27) ggest that this "metaplastic epithelium" which results from the healing an ulcer might possess greater resistance to acid than normal.

Factor of Exposure to Irritant Drinks. Cohnheim (71) and, more cently, we (72) found that when the stomach of the dog is filled with a misolid, pasty mass of food, such as raw ground meat, water tends to low the lesser curvature to the duodenum. We (72) found that approxi- ately 70 per cent of water swallowed soon passed from the duodenal tula of a dog, the remainder being mixed with the food in the stomach. his is a more crucial type of experiment than those in which barium is ven, barium being a heavy material affected readily by gravity.

The literature on the effect of corrosive poisons of a fluid nature on the omach of the dog and man support the original observation of Cohnheim. he extensive literature on this subject is reviewed by Redwitz (5) and erkel (73). The observations show that the part of the mucosa injured pends on the degree of filling of the stomach and on the character of the stric contents. In the case of the empty stomach, either the entire gastric ucosa is corroded, or only the lesser curvature and all of the pyloric ntrum are chiefly affected. In this latter case, when it happens, it appears at the oblique musculature of the stomach contracts so as to shunt the rrosive fluid into the pyloric antrum. When the stomach is filled with a uid food, all of the gastric mucosa is corroded. When the stomach is filled ith a semisolid pasty mass, the lesser curvature and pyloric antrum are iefly affected. The most frequent complication in those patients who cover is pyloric stenosis (75). So, when the stomach is filled with a misolid pabulum, the lesser curvature and prepyloric region receive ost of the insult from irritating drinks.

Factor of Exposure to Mechanical Injury: *Pressure from Outside the omach and Duodenum.* Schwartz (11) pointed out that most of the gastric lcers occurred in that portion of the stomach (at and just proximal to the ncisura angularis) which was compressed by the natural body waist. umerous pathologists (see Redwitz) have suggested that the liver, ancreas, vertebral column, and aorta might compress either the duodenal ulb or the mid-portion of the stomach, or both. It was also suggested that ressure on the duodenum where it crossed in front of the vertebral column ould cause stasis in the duodenal bulb and duodenal ulcer. In view of the obility of the duodenal bulb, as demonstrated by roentgenologic

examination on changes in posture, it is difficult to accept such argument.

The tight lacing of corsets is the best example of the production external pressure on the stomach. The effect of this on the incidence gastric ulcer in women has been discussed elsewhere (p. 488 et se On the basis of necropsy evidence, such exaggerated external pressure d increase the incidence of gastric, but not duodenal, ulcer. Since vertical portion of the lesser curvature tends to be more in line with vertebral column than the greater curvature, this would tend to exp the former to greater mechanical trauma than the latter.

Pressure from Inside the Stomach. The possibility that the disposition intragastric pressure may be a factor in causing gastric ulcer to be loca in the lesser curvature and prepyloric regions has engendered much disc sion in the German literature. This was emphasized particularly Aschoff, who pointed out that the prepyloric region and the reg proximal to the incisura angularis (isthmus of Aschoff) is exposed to extra mechanical load. Examination of the evidence indicates that if is a factor, it is a minor one.

It has been found by Quigley (76) that when a peristaltic wave pa over the stomach, the pressure in the prepyloric region is greater tha the region of the corpus. That is, a pressure gradient toward the pylo exists. It has also been demonstrated, by placing an opaque pill in stomach and viewing the movement of the pill roentgenologically, that peristaltic wave compresses contents toward the pylorus, some or all of contents pass cephalward and may do so with considerable speed. Th is no evidence, however, that the force of the propelled chyme or of eddy currents is directed against the lesser curvature more than aga the greater curvature and the prepyloric mucosa. In fact, it would s reasonable to believe that the prepyloric mucosa would be more expo to pressure effects than the lesser curvature.

Aschoff (19) proposed and defended the concept that most gas ulcers are located proximal to the incisura angularis because a zon constriction exists in that region of the stomach. He studied the f of the stomach immediately after the death of soldiers during World Wa and found an "isthmus" or a zone of constriction between the corpus pyloric portions of the stomach measuring from 2 to 5 cm. in length. P to his report, a number of observers had suggested, both on anatomic roentgenologic grounds, that a sphincter antri pylori exists at the incis angularis; this has not been established physiologically.

Aschoff's reports and those of his colleagues gave rise to a contro which led to an increase in our knowledge of the form of the stomach failed to establish the existence of an "isthmus." If an "isthmus"

st, it would not explain why the ulcer develops on the lesser curvature
d not the greater curvature.

If internal gastric pressure does serve as a chronicity factor in gastric
er, some other factor must cause localization of the ulcer in the region
the lesser curvature.

Factor of Relative Fixation of the Lesser Curvature. It has been
gued that the relative fixation of the lesser curvature would expose it (a)
the effect of the trauma of a pressure gradient, eddy currents, and
istaltic activity, or (b) to interruptions of venous blood flow during
istalsis, or (c) to spasm of the blood vessels. It has also been argued that
ing of the stomach stretches it longitudinally and places tension on the
od vessels present in the lesser omentum, which inserts into the lesser
vature and supports the stomach.

Factor of Motility of the Stomach. Since the lesser curvature is
nsiderably shorter than the greater curvature, the contraction persists
ger at all sites on the lesser curvature. This is especially true of the
ves of contraction when they are at or just cephalad to the incisura.
e contractions of the lesser curvature at this site when viewed directly
roentgenologically appear to "stand" there for a brief period. In fact,
location of ulcer at and proximal to the incisura has been explained
due to the "standing wave" of contraction at that site (Orator), because
relative fixation of the lesser curvature exposed it to a greater inter-
ence with blood flow.

It has also been pointed out that when the defect in the mucosa pene-
tes to the muscularis propria, connective tissue binds the margin of the
er to the muscularis. Hence, the surrounding muscularis propria finds
new insertion into the scar. This exposes the margin of the ulcer to
chanical manipulation and interference with its blood supply in con-
quence of the stretch resulting from the filling of the stomach and
ristaltic activity.

Factor of Mobility of the Gastric Mucosa on Underlying
ructures. The extent to which the mucosa is attached to the under-
ng muscularis propria and the activity of the muscularis mucosae and
astic tissue will determine the extent to which a defect in the mucosa
ll gape. Inspection of the stomach soon reveals that the mucosa of the
loric portion of the stomach is more firmly attached to the muscularis
opria than in the fundus. Schmidt (78) found that the surface of the
ucosa was 45 times greater than the underlying contracted muscularis
the fundic portion in the stomach and only two times greater in the
loric portion.

It has been shown that an excision ulcer in the fundic mucosa heals
ore readily than one in the pyloric (p. 147). This would predispose to

ulcers in the pyloric mucosa, but has no crucial bearing on the localizat of ulcer on the lesser curvature, since the mucosa there is no more fi than in the prepyloric region.

Significance of the Form of the Ulcer in the Lesser Curvatu The form of a chronic or penetrating ulcer has been extensively discus in the German literature, particularly in relation to the mechanical a vascular factors.

The *terraced ulcer* indicates the extension of an ulcer at the level of mucosa. The *indolent ulcer* indicates poor proliferation of epithelium at margin, a diminution of inflammation of the margin and base, a exhaustion or a lack of secondary contraction of connective tissue. T *round or oval ulcer with a globular base* and an overhanging margin is the t of ulcer which would heal readily if the mechanical and acid factors w decreased. Such an ulcer forms in the pyloric pouch of the dog when excision ulcer is roughly manipulated (79). On healing, the overhang margin disappears by filling in with connective tissue. Some ulcers bec elongated and straddle the lesser curvature to produce what is calle "saddle ulcer." The "saddle ulcer" is believed to represent the exten of a single lesser curvature ulcer rather than the confluence of an u on the anterior and another on the posterior wall.

There are two types of so-called "funnel ulcers." In *one type*, the of the funnel tends to be perpendicular to the surface of the mucosa. T type is found in subacute and active chronic ulcers in which the u appears to be penetrating to the serosa. This is the type of ulcer wh Hauser (3) used to support his infarct theory of peptic ulcer. Sometim bleeding or thrombosed vessel can be found at the apex of such a fun shaped ulcer. In *the second type*, the axis of the funnel tends to parallel lesser curvature, the apex of the funnel being directed toward the car This ulcer is characterized by a heaped-up undermined margin on cardiac side and a flat margin on the pyloric side. The existence of type of gastric ulcer was emphasized by Aschoff (19) and Stromyer (who explained it as due to the pyloricward movement of the gastric c tents which tend to flatten out the pyloric margin. Some failed to find type of ulcer (9), and others (3, 5, 30) observed it occasionally, tho the apex was not uniformly directed toward the cardia. In some case ulcer of the descending part of the lesser curvature, the apex of the u is directed toward the pylorus. This flattened funnel type of ulcer is u as an argument in favor of the action of a mechanical factor.

The Phylogenetic Factor. Bauer (84) and others (5) view corporic portion of the lesser curvature (that part proximal to the inci angularis) as being analogous to the gastric trough of ruminants. T consider the "magenstrasse" in man as a rudimentary structure, like

pendix, and hence more subject to disease. Though interesting specula-
n, it does not teach us why it is more subject to disease.

Duodenal Bulb

Very few authors consider why duodenal ulcers are almost in every
tance located on the anterior or posterior wall or both. Those who do
nsistently assume that the ejected chyme strikes either the anterior or
sterior wall and that this mechanical factor is involved. It really is not
own whether the stream of chyme strikes the superior, inferior, anterior,
posterior wall. Neither is it known whether the anterior and posterior
lls are relatively avascular as compared to the superior and inferior
lls, except that when the gastrohepatic ligament is pulled an anemic
ot appears on the anterior wall.

It is commonly agreed that 95 per cent of duodenal ulcers are located
the first 3 cm. of the duodenum because of several factors. This region
s a relatively poor blood supply. It is exposed to the brunt of the
emical and mechanical action of acid chyme because it is the passageway
all the acid secreted by the stomach and, since the duodenal bulb is
ed most of the time during the gastric digestion of a meal, it is more
nstantly exposed to acid of higher concentration than the remainder of
e duodenum.

Postoperative Jejunal and Gastrojejunal Ulcer

The statement is frequently made that the jejunal ulcer occurs at the
int at which the ejected stream of chyme strikes the wall of the jejunum.
here is really no good evidence to support this statement. It has never
en shown which wall of the jejunum the chyme strikes. It is frequently
ted that the jejunal and gastrojejunal ulcer both occur on the anterior
all most commonly (5). This statement is made without considering
hether the anastomosis is of the anterior or posterior type. It would seem
ld that the ulcer should occur most commonly on the anterior wall in
e case of both types of gastrojejunostomy. It would not be so difficult
explain if the ulcer occurred most commonly on the posterior wall of a
osterior gastroenterostomy and on the anterior wall of an anterior
astroenterostomy, since the respective walls would appear to be more
one to distension and partial interruption of the blood supply as a
sult of a rise in intragastric pressure and the ejection of chyme.

The following factors are considered in the pathologic and surgical
erature as being responsible for the cause of gastrojejunal (marginal)
cer. (a) Gastric contractions tend to erode mechanically the mucosa,
interfere with the blood supply, or to evaginate the stoma into the
omach, which combines both of these factors. (b) The mucosa over the

suture line is fixed to the connective tissue below and, hence, is subject to trauma and has a poorer blood supply. (c) The use of nonabsorbable suture material acts as a foreign body to stimulate connective tissue formation, which for reasons just stated decreases the resistance to the corrosive action of gastric chyme. In support of this, it is pointed out that if one sews silk sutures in and out of the muscularis propria at the site of an excision ulcer, the healing of the ulcer is retarded and it may become chronic (see p. 157). (d) Poor tailoring of the stoma leaves a gaping wound or invaginates a finger of mucosa, both of which, if considerable connective tissue proliferation is present, will predispose to the formation of a chronic ulcer. (e) The use of clamps, by injuring the mucosa, causes an acute ulcer which later becomes chronic. (f) Inadequate hemostasis leads to hematoma formation, connective tissue proliferation, and ulcer formation. Of course, the susceptibility of jejunal mucosa to acid injury, acid chyme, infection, and the "ulcer diathesis" are hypothetically ascribed as the cause of gastrojejunal and jejunal ulcer.

The statistical evidence in the pathologic and surgical literature does not establish any of these factors as being crucially concerned.

Wright (32) makes a very interesting observation relative to the symptom of pain and the healing of an anastomotic ulcer when a stoma into the colon forms. Pain was completely absent in 15 of 40 cases, slight in eight, and prominent in 13. He explains the absence of pain as due to the healing of the ulcer. This would indicate that stasis of acid contents in the jejunum was a factor in causing the ulcer.

Sites of Predilection in Animals

Observations on the location of ulcers which occur spontaneously or experimentally in animals should indicate whether the site susceptibility in animals is similar to that in man. Such observations may have a direct bearing on pathogenesis.

Location of Spontaneous Ulcers in Animals

Spontaneous ulcers in animals most commonly occur in the stomach and are associated with some type of gastric irritation. In the 14 peptic ulcers found by Fox (22) in animals dying in a zoo, all occurred in the stomach and eight were located on the lesser curvature.

Location of Experimental Ulcers in Animals

It is unfortunate that the experimental literature in so many instances, including most of our own articles, fails to give the location of the

tomach or duodenum. Some articles do not state clearly how many
peptic ulcers" reported occurred in the stomach or duodenum.
Table 42, we have summarized some of the more recent and leading
, which provide some evidence on this point. It will be noted that
w even in this group give definite information on the site.

LECTIVITY OF ULCEROGENIC PROCEDURES FOR THE STOMACH OR
STUM. *Gastric ulcer* predominates after cinchophen and caffeine
stration (cat) and after bilateral vagotomy (rabbit and dog) and
deficiency (dog). It also predominates when cirrhosis of the liver
is produced by amidoazotoluol. *Duodenal ulcer* predominates after
d skin burns, excessive secretion of acid, biliary and pancreatic
bstruction (complete and partial), and biliary fistula in the dog.
illess of the predominating trends, peptic ulcer due to these causes
ccur in either or both organs, except in the case of vagotomy ulcer,
occurs only in the stomach.

LECTIVITY OF ULCEROGENIC PROCEDURES FOR REGIONS WITHIN THE
CH. The *vagotomy ulcer* in the rabbit most closely resembles that of
s regards its location on the lesser curvature in relation to the
a angularis. The *cinchophen and caffeine gastric ulcer* (gastritis) is
ntially located in the pyloric portion of the stomach 1 to 3 cm.
nal to the duodenum (dog) and is about equally distributed between
er curvature and posterior wall. The cinchophen ulcer tends to be
prepyloric than the vagotomy ulcer. The *acid gastric ulcer* (gastritis)
erentially located in the same region as the cinchophen ulcer, the
nal mucosa being more susceptible to acid and the pyloric mucosa
susceptible to cinchophen.

LECTIVITY OF ULCEROGENIC PROCEDURES FOR REGIONS WITHIN THE
NUM AND JEJUNUM. *Acid duodenal ulcer* occurs most frequently on the
or wall. In fact, we have gained the impression based on anatomic
ation that when two duodenal ulcers ("kissing ulcers") are present,
e of the posterior wall is older. This is particularly interesting be-
the postoperative jejunal ulcer in the M-W dog is chiefly an acid
nd always occurs on the posterior wall.

PLANATION OF THE LOCATION OF EXPERIMENTALLY INDUCED ULCER IN ANIMALS

ne type of liver damage is common to all these causes of ulcer,
as far as we know, the ulcers due to caffeine, vagotomy, and the
ve secretion of acid.

d gastric ulcer arises on an exogenous type of chemical gastritis. The
phen, caffeine, and acid gastric ulcers are located in approximately

Table 42

SHOWING THE SITE AT WHICH EXPERIMENTALLY INDUCED GASTRIC AND DUODENAL ULCER OCCURS

Procedure	*Reference No.*	*Animal*	*No. Animals Used*	*Stomach No. of Ulcers*	*Lesser Curvature*	*Remarks*	*Both Duodenal and Stomach*	*No. or Per Cent Ulcer*	*Duodenum*			
									Anterior Wall	*Posterior Wall*	*Both Walls*	*Remarks*
Cinchophen	86	dog	43	43	1, c. & post. wall of prepyloric region		4	4				Same 4 ulcers
Cinchophen	87	dog	34	34	9	15 others not located	8	8	2	5	1	Same 8 ulcers
o-aminoazotoluol	88	dog	?	10		Hepatic cirrhosis	3	2				
Burns	89	dog	28	0				22				
Burns	90	man	92 cases	16			5	71				
Caffeine	91	cat	22	11	4	Jejunal lesions 2 duodenal ulcers		9				Lesser curvature, prepyloric & pyloric regions
Histamine in Beeswax	92	dog	20	2		Prepyloric		12		Chiefly ?		
Histamine in Beeswax	85	dog	33	4	—	Prepyloric	3	10		Chiefly		
Histamine I.V.	87	dog	25	8	2	Chiefly	1	32	1	—	1	Lesions in 2 cases

Biliary Obstruct.	96	dog	64	1	all							
Partial Biliary Fistula	97	dog	43	0								
Pancreatic Obstruct.	98	dog	61	0								
Vagotomy	99	rabbit	29	12	all							
Vagotomy	100	dog	13	2								
Vagotomy	101	dog	6	2	2							
Hypophysectomy or Brain Lesions	102	dog	23	1								
Protein Deficiency	103	dog	32	13	—	Fatty liver						
Protein Deficiency	104	dog	22	3	1							

the same region. The cinchophen ulcer is made worse by rough fo (bones) (59) and better by antacids and emollients (mucin) (p. 29 A pyloroplasty reduces the incidence of cinchophen ulcer by preventi those ulcers which would otherwise occur in the pyloric canal (2 Caffeine and acid ulcer would undoubtedly be made worse by rou foods, but the effect of pyloroplasty is conjectural. Nevertheless, *it appe that gastric ulcers due primarily to an exogenous or endogenous gastritis-produc agent tend to be located more distally in the stomach than those which are due prima to the stasis of rough food (vagotomy). Both tend to select preferentially the reg of the lesser curvature and posterior wall.*

Just why a disturbance of the liver predisposes to peptic ulcer, p ticularly duodenal ulcer, is conjectural. There is no evidence for existence of a hypersecretion of acid or for a hyposecretion of Brunn glands. Since the exclusion of bile predisposes to duodenal ulcer m than the exclusion of pancreatic juice, which is a more alkaline flu either the liver is involved or bile contains some special ulcer prevent property than that of an antacid. Perhaps the liver produces someth necessary for the normal functioning of the mucosa.

The *vagotomy ulcer*, which is primarily a lesser curvature ulcer, is chiefly to stasis and rough food. This indicates that mechanical irritat by rough food is an etiologic factor for the ordinary lesser curvature u in man. The *cinchophen gastric ulcer* and the *caffeine gastric ulcer* cause endogenous type of chemical gastritis.

It is of interest to note that the endogenous inflammation produ by cinchophen and caffeine do not suppress acid secretion, in fact, caffe definitely stimulates it, and does not tend to extend beyond the pylo whereas the exogenous inflammation caused by acid extends beyond pylorus and is more severe distal than proximal to the pylorus (grad of susceptibility to acid, p. 221). It is possible that the agent released burns is relatively specific for producing an inflammatory or angiot effect in the duodenal, as compared to the gastric, mucosa.

The effect of protein deficiency would seem to be related to the esser importance of protein in renewing cells and healing. This may be an to explain why the ulcer tends to be located in the stomach rather t the duodenum, the wear on the gastric mucosa perhaps being gre than that on the duodenal. The tendency of the protein deficiency ulc occur in the stomach of the dog does not fit in with the high-rate of d denal ulcer in the South Indians, who live principally on tapioca, rice, "pepper" curry, or a low protein, low vitamin diet.

There is no good explanation for the marked preferential occurr of acid ulcer on the posterior wall of the duodenum and of the jeju after gastrojejunostomy in the dog. Since the ulcer occurs on the poste

l of the gastrojejunostomy when performed end to end or end to side, factor of tugging on the blood supply and of the nozzle action of the orus would seem not to apply.

In these experimentally induced ulcers which morphologically simu- spontaneous ulcer in man, we find agents or procedures (a) which duce an endogenous inflammation of the pyloric or duodenal mucosa ffeine, cinchophen, infected burns), (b) which produce an exogenous ammation of the pyloric or duodenal mucosa (acid), (c) which provide essive mechanical irritation represented by stasis and rough food gotomy), (d) which impair the supply of nourishment for repair otein deficiency), and (e) which impair hepatic function.

Repair and Healing in the Region of the Lesser Curvature

It has been indicated elsewhere that an excision ulcer in the fundic cosa heals more rapidly than one in the pyloric and one in the pyloric re rapidly than one in the duodenal. This has been extended to a com- ison of the rate of healing of an excision ulcer in the lesser curvature that of the mucosa elsewhere in the pyloric region. Yano (33) and rton (40) have reported that an excision ulcer of the lesser curvature ls more slowly. Nicolaysen (41) has also observed that in the vago- nized rabbit an excision ulcer on the anterior wall will heal while a onic ulcer is forming on the lesser curvature. Though the data in these icles do not permit a quantitative conclusion, they do qualitatively ablish that *an ulcer on the lesser curvature does not heal as readily as elsewhere the stomach.*

Vascular Tugging and Other Factors in Relation to the Vulnerability of the Lesser Curvature

Jejunal patches have been placed in the posterior and anterior wall the pyloric region and in the fundic region (p. 105). Patches so placed good surgical procedure have not ulcerated. In one laboratory (46, 70,), patches of jejunum were placed in the posterior and anterior wall of stomach in 22 dogs. One ulcer of the suture line occurred. In 38 jejunal tches placed saddle-wise (70) in the lesser curvature, four ulcers (10 per nt) occurred. In five dogs with lesser curvature patches, three developed ers of the patch after a M-W operation (p. 105) was performed; whereas eight dogs with patches elsewhere in the stomach, none developed ers of the patch after the M-W operation. Evidently, a jejunal patch the lesser curvature is more vulnerable than a patch elsewhere in the mach to the continuous hypersecretion and disturbed nutrition most -W dogs manifest unless given a special diet. Tugging on the blood

vessels of the patch in the lesser curvature was thought to be a fac increasing vulnerability.

Comment

These experiments on healing and jejunal patches do not reveal w the lesser curvature position is more vulnerable. They demonstrate t something in addition to the presence of normal stresses, such as a hy secretion and disturbed nutrition, definitely increase the vulnerabi of the lesser curvature position. They demonstrate further that the le curvature is a vulnerable area in a species which is relatively non ceptible to peptic ulcer and lacks a so-called "constitutional predisp tion." Adequate experiments would probably demonstrate the same the prepyloric region, just as the instillation of acid into the stomach demonstrated that the first 2 or 3 cm. of the duodenal mucosa is relati more susceptible than the gastric mucosa.

Other Anatomic Items

Number of Peptic Ulcers in a Single Specimen

Number of Gastric Ulcers in the Same Stomach. Chronic gas ulcer occurs singly as a rule. Stewart, in 200 autopsy cases of gastric ul saw only five (2.5 per cent) in which two ulcers were present. In 172 c of partial gastrectomy, only two cases (1.1 per cent) of double ulcer w found.

Acute gastric ulcers are generally multiple. They occur singly in f 10 to 20 per cent of autopsy cases, according to many reports cited Redwitz (5) and Hauser (3).

Subacute ulcers are single in one half the cases, according to Stew (1).

Number of Ulcers in the Same Duodenum. Two open chronic ul ("kissing ulcers") are found rather frequently at autopsy (17 per cen cases; Table 41). Perry and Shaw in 1893 (81) collected 160 autopsy c of duodenal ulcer and found multiple ulcers in 14.4 per cent. Hauser in 1926 collected 547 cases from German authors and found an incid of 20.3 per cent of multiple ulcers. Acute ulcers were included in som the reports used by Hauser, which accounts for the higher percentag

According to Stewart (1), single acute ulcers are seen more freque in the duodenum than the stomach (single in only 19 of 40 cases), they rarely number more than six or eight.

Thus, multiple chronic ulcers are more common in the duode than the stomach.

SOCIATION OF ACUTE AND CHRONIC ULCER. It is not uncommon for and chronic ulcers to coexist in the stomach or the duodenum. This in about 6 per cent of cases of gastric ulcer and 12 per cent of cases odenal ulcer.

SOCIATION OF CHRONIC ULCER OF THE STOMACH AND OF THE DUO-M. Chronic ulcer or scarring of both the stomach and duodenum s frequently enough to have some significance. It was found in 5.5 ent (21 cases) of 4000 autopsies by Stewart in which there were hronic gastric and 230 chronic duodenal ulcers. Wilkie (21) found onic ulcer in both organs in 14 per cent or 42 of 300 surgical cases. ccasionally, a chronic ulcer may be found in one organ and acute or erosions, probably terminal in nature, in the other organ.

GNIFICANCE OF THE DISCRETENESS OF PEPTIC ULCER. Because of the nscribed nature of a peptic ulcer, Virchow (82) rejected the corrosive n of gastric juice as a primary cause. He argued reasonably that, if were the primary cause, the entire mucosa exposed would be cor-, which does occur after death. He believed that a local vascular bance or insufficiency was responsible for a *locus minoris resistentiae.* hen acid is introduced into the stomach continuously in quantities ient to cause injury, circumscribed ulcers occur. They can occur only se the threshold of the capacity of the cell to neutralize the acid is ded, and the capacity of the cell to neutralize the acid is dependent rt on the blood supply and in part on the capacity of the cell to er antacids from the blood to the exposed part of the cell membrane. apacity of a local group of cells to transfer antacid from the blood be due to many causes. Once the acid penetrates, it may injure the a of the blood vessels and impair the blood flow. The focal nature eration is characteristic of all epithelial membranes. In the stomach duodenum or jejunum, the acid first destroys the weakest or most y exhausted locus of cells.

SIZE OF PEPTIC ULCERS

ZE OF GASTRIC ULCERS. The size of chronic gastric ulcers varies derably. Data from Leeds, England, and the Mayo Clinic, Roches-Minnesota, are shown in Table 43. In the former series, 85 per cent less than 2.5 cm. in diameter and in the latter 93 per cent. It is of st to note that the larger ulcers were found at autopsy.

is rare for a benign gastric ulcer to be larger than 3.7 cm. in diame-larger, it is almost certain to be a carcinomatous ulcer. Approxi-y 23 per cent of carcinomatous ulcers are within the size of benign , i.e. 3.7 cm. or less in diameter (83).

No correlation between the age and size of the ulcer was found Alvarez and MacCarty (83).

Size of Duodenal Ulcers. Chronic duodenal ulcers tend to smaller than gastric ulcers (Table 43; postmortem cases). Most duoden ulcers do not measure more than 2.5 cm. in diameter (77). According Stewart (1), posterior wall ulcers tend to be larger (16.6 × 12 mm average) than those on the anterior wall (11 × 8 mm. average). This, suggests, is due to the greater tendency of anterior wall ulcers to perfora and posterior wall ulcers to become chronic. Duodenal ulcers of large si occur only on the posterior wall (1).

Comment. Why should the upper limit of a gastric ulcer be 4.0 cm Why should a duodenal ulcer tend to be smaller than a gastric ulc These questions are related to the question pertaining to the cause the circumscribed nature of an ulcer.

Table 43

Size of Chronic Gastric and Duodenal Ulcers*

Greatest Diameter in Mm.	*Gastric Ulcer*		*Gastric Ulcer*	*Duodenal Ulcer*
	Stewart, Leeds, England		*Alvarez & MacCarty*	*Stewart, Leeds*
	Postmortem Cases	*Surgical Specimens*	*Surgical Specimens*	*Autopsy*
Under 12.5	9 } 48.5%	60 } 85.3%	} 602 (93.8%)	21 } 74.3
12.5 to 25	25 }	73 }	}	31 }
25 to 50	17	23 (14.7%)	36 (6.2%)	18
50 to 75	9	..	..	..
75 to 100	6	..	..	..
100 to 125	4	..	..	..
Total	70	156	638	70

* There were two cases in the Mayo and one in the Leeds series where the u measured 4 cm. in diameter. Note the size of the ulcer at autopsy tends to be la than at surgery.

The average diameter of the surgical specimens was 16 × 10 mm. Chronic ga ulcers according to MacCarty usually vary from 1 to 40 mm. in diameter and 1 to 20 mm. in depth; and duodenal ulcers vary from 1 to 25 mm. in diameter 1 to 5 mm. in depth.

Several explanations may be offered in answer to these questi Both gastric and duodenal ulcers are limited in size because, except w very calloused or indolent, as they increase in size the hazard of perfora

morrhage occurs and dramatically brings an end to the extension. as they increase in size, they cause more distress and this forces the nt, even the animal, to diet and rest. This would also explain the er size of the duodenal ulcer, since it causes distress more readily gastric ulcer; for example, clinically, duodenal ulcer predominates gastric ulcer, though at autopsy the incidence is practically the same.

Form and Histologic Characteristics of a Peptic Ulcer

hese features of peptic ulcer have been described adequately else-e: the form on page 52, the histology on pages 142 to 146.

ecurrence of Peptic Ulcer at the Site of a Previous Scar

he pathologic literature is at variance regarding whether an ulcer s at the site of the scar of a preceding ulcer (3, 5). This is a question n would obviously be difficult to establish by the study of surgical or psy specimens in man. In fact, pathologists have argued for and ist this possibility and point out that the mucosa overlying a scar be less vulnerable because it may be less susceptible to the effects of ular spasm and trauma due to muscular spasm. Perforations have red at the site of a previous one as identified by a suture; the suture have been the cause of the selection of the same site.

his is a problem best solved by animal experimentation. In dogs, an ion ulcer of the stomach has been made, allowed to heal for four s, and then histamine in beeswax was given. In every case, an ulcer oped, but never in the scar left by the excisional ulcer (85).

Extension of the Ulcer

xtension to the Serosa. The serosa external to the crater of the ic or duodenal ulcer in the living subject is thickened and opaque a larger area than the crater. In an active ulcer, the blood vessels of erosa of the affected area are engorged as well as those of any ad-ns which may be present. In the area just external to the crater, pin or patchy hemorrhages may be present or easily elicited by stroking a piece of gauze. Edema of the area is evident in some cases. In old ed ulcers, the scar is white, anemic, and sclerotic.

he serosa external to an *ulcerated cancer* appears much like that of an . Otherwise, the serosa external to a cancer is marked by a plaque hite firm tumor tissue if the tumor has penetrated to the serosa. The cent lymph glands are enlarged and firm in both diseases, but on section the cancerous gland shows white nodules of tumor and the med gland is pinkish or greyish.

Extension to Adjacent Organs

The pancreas frequently forms the floor of a gastric ulcer on posterior wall of the stomach. Anterior wall gastric ulcers more freque involve the liver. In autopsy and surgical specimens, the pancrea involved in from 17 to 25 per cent of the cases and the liver in 2.0 to per cent. The pancreas and liver both are involved in approximately per cent of the cases. In addition to the pancreas and liver, the transv colon, left kidney, and adrenal may rarely become involved in poste wall ulcers and the abdominal wall in anterior wall ulcers (1, 3, 5).

The head of the pancreas is frequently involved in posterior duodenal ulcer. Only rarely, however, is the pancreas or liver actu seen in the floor of the ulcer, unless it is quite large. In some cases, scar tissue forms in such a manner as to cause a diverticulum whic called a "pseudodiverticulum."

Adhesions

Adhesions are found at autopsy in 40 to 45 per cent of cases of ga and duodenal ulcer (3, 5).

Gastric ulcers on the posterior wall are associated with adhes in the small sac of the peritoneum and pancreas. Anterior wall ga ulcers form adhesions to the liver, abdominal wall, spleen, gall blad and colon. In posterior wall ulcer of the duodenum, the pancreas duodenum become fused by a layer of connective tissue. Anterior duodenal ulcers form adhesions to the liver, gall bladder, and co they form adhesions less commonly because they tend to heal or perfo early (Hauser).

Summary

The majority of gastric ulcers occur on or within one inch of the l curvature. They appear to concentrate first in the region of the inci angularis and just proximal to it in both men and women, and secon the prepyloric region, chiefly in men. Whereas gastric ulcer occurs ch in relation to the lesser curvature, gastric cancer occurs chiefly in rel to the prepyloric region.

Anterior wall perforation decidedly predominates over posterior perforation, and ulcers in the prepyloric region are most likely to perfo Fatal hemorrhage is more likely to occur from an ulcer of the lesser cu ture, or posterior wall of the stomach and duodenum.

Duodenal ulcers are usually located on the anterior or posterior and only rarely on the mesenteric or antimesenteric border. Ninety per cent are located within the first 3 cm. and especially within the 1.5 cm. of the duodenum.

Following gastroenterostomy, ulcers may form at the anastomotic or in the jejunum, the former being called marginal or gastrojejunal

latter jejunal. An ulcer on the gastric side of the anastomosis is rare. y are rarely located more than 3 cm. from the stoma.

Acute and chronic peptic ulcers may occur in the esophagus, but ly if ever in the presence of cardiospasm. Heterotopic gastric mucosa Meckel's diverticulum or in the esophagus may secrete enough acid to se peptic ulcer.

A number of factors may be concerned in causing ulcer to be located ferentially in relation to the lesser curvature and prepyloric region. s evidence shows that excision ulcers of the lesser curvature heal more ly than elsewhere in the stomach and that a jejunal patch placed in lesser curvature is more prone to ulcerate. Mechanical and vascular ors appear to be the most important in predetermining the lesser vature and prepyloric region for ulcer formation.

The more prolonged contact of acid chyme and the relatively poor od supply appear to be the reasons why the first 1.5 cm. of the duo- um ulcerates so commonly.

The factors which predispose to jejunal and marginal ulcer are dis- sed. Poor tailoring of the anastomosis, we believe, is an important or predisposing to marginal ulcer. Jejunal ulcer is due principally to inherently low susceptibility of jejunal mucosa to acid chyme.

In animals, experimental gastric ulcers are more common following chophen and caffeine administration, bilateral vagotomy, and protein iciency and cirrhosis of the liver induced by amidoazotoluol. Duodenal ers are more common after infected skin burns, excessive secretion of tric juice, biliary and pancreatic duct obstruction, and biliary fistula.

Acute gastric ulcers are usually multiple and chronic gastric ulcers ally single. Acute duodenal ulcers are often single and chronic duo- nal ulcers are often multiple. Six to 14 per cent of peptic ulcer patients ve both a gastric and a duodenal ulcer.

Approximately 90 per cent of gastric ulcers are less than 2.5 cm. in meter. It is rare for a benign ulcer to exceed 3.7 cm. in diameter, but proximately 23 per cent of malignant ulcers are less than 3.7 cm. in meter. Gastric and duodenal ulcers may extend into adjacent organs. netration into the head of the pancreas by posterior wall duodenal ulcer very typical.

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CHAPTER 16

Complications in Relation to Pathogenesis

Introduction

The most common complications of peptic ulcer are hemor perforation, and stenosis, in their order of frequency. In order of mor they are perforation, hemorrhage, and stenosis. There is no good why stenosis should ever cause death.

An idea of the relative frequency of these three complications m gained from the following references. Emery and Monroe (1) fo 1435 patients with peptic ulcer for an average of 3.9 years (23 per ce six or more years), and found an incidence of 7.7 per cent (111 ca perforation with a mortality of 1.9 per cent (28 cases), of 26.7 pe (384 cases) of manifest hemorrhage with a mortality of 1.3 per (20 cases), and an obstruction in 11.7 per cent (169 cases) with a mo of 0.2 per cent (four cases).

Deformities Due to Scars

Stomach. When a large gastric ulcer heals it leaves a radiate which is quite characteristic. The scar left by a small ulcer is not easily

An ulcer which is large and straddles the lesser curvature on h may cause an hourglass contraction of the stomach. This hourglas traction, in contrast to one due to spasm in the presence of an active does not yield to medical treatment. This is the most frequent def which occurs in the stomach because of the high incidence of lesser ture ulcer. In 173 cases with gastric ulcer and scar, it occurred w frequency of 9.8 per cent (2).

Several clinics in England have reported a marked decrease incidence of high grade cicatricial deformities of the stomach (3, 4 incidence had been greater in females than males, and the dec the incidence of deformity has been explained as due to the decrease incidence of gastric ulcer in females under 30 years of age. It ha suggested that women are more prone to develop this deformity b a woman follows management better.

Duodenum. *Pyloric stenosis* of duodenal origin is more comm that of gastric origin. It may be caused by the spasm and edema asso

active ulcer and yield to medical treatment, or it may be due to
al contraction. The cicatricial contraction may cause stenosis of
denum or of the pylorus. In 230 cases of chronic duodenal ulcer
rs, cicatricial stenosis of the pylorus occurred in 15.6 per cent and
ial stenosis of the duodenum occurred in 7.4 per cent (2). Emery
nroe (1) followed 1435 cases of peptic ulcer for an average of 3.9
nd observed an incidence of 11.7 per cent (169 cases) of pyloric
tion. In an autopsy series, Portis and Jaffe (5) found an incidence
sis of 11.8 per cent.

some instances, a duodenal ulcer will heal and the scar will pull
loric ring and duodenal bulb together, so that a pouch will be
on each side of the scar in the duodenal bulb. In the roentgeno-
sis may simulate a protrusion or hernia of the mucosa of the pyloric
nto the duodenum.

e form of cicatricial obstruction in chronic ulcer of the stomach
denum occurs in 20 per cent of cases (382 cases) and is severe in
cent (2). So, this complication is quite frequent in occurrence.

Perforation

te perforation is the most dangerous complication of peptic ulcer.
h its total incidence is relatively small, it is a common condition on
ergency service of a large metropolitan hospital. The mortality has
ly decreased since the introduction of the sulfa drugs and anti-
In the future, the mortality will be less than shown in the data
ted here.

General Incidence

e would like to know the chances of perforation in a patient with
ulcer. An exact answer to this question cannot be had because,
be seen from the following presentation, many factors are involved,
the most important today being the sex and another the care the
devotes to the management of his disease. It is not surprising,
all factors are considered, to find that the literature answers the
ng question with figures ranging from 1 to 28.1 per cent (5, 41, 42),
ling on the conditions under which they are collected.

best data regarding the incidence of perforation in peptic ulcer
s should be derived from a large group of patients followed over a
of years. Only a few series of data from such a source are available.
and Monroe (1) followed a group of 1435 ulcer patients for an
period of 3.9 years (23 per cent were followed six or more years),
nd that 7.7 per cent developed perforation. Flood (6) followed 233
atients for an average of 6.9 years. Two or 0.9 per cent developed

perforation during this period; when the past history was included, the overall average was 3.4 per cent. Hurst and Stewart (2) observed an overall incidence of 3.0 per cent in 164 patients seen over a period of seven years. The German literature (7) indicates that 10 per cent of all peptic ulcer patients perforate sooner or later. This latter figure would probably be too high for a group that followed management, since Emery and Monroe (1) found a much higher incidence of perforation in a nontreated group. It would appear that in a well-managed group the incidence of perforations should not be larger than 3 or 4 per cent over a period of five years.

A truer picture of the actual incidence, as seen by the physician, is obtained from the percentage of perforated cases in relation to all ulcer cases admitted to a large number of hospitals. This figure will actually be too high because all patients with peptic ulcer are not admitted to a hospital. In a series of 33,439 hospitalized cases of peptic ulcer collected by De Bakey (8), there were 4410 cases, or 13.2 per cent, admitted for acute perforation. During a comparable period, the percentage incidence of perforation among the patients admitted for peptic ulcer in Sweden (9) was 18.1 per cent; St. Thomas Hospital, London, 14 per cent (10); Cook County Hospital, Chicago, 14 per cent (5); and Charity Hospital, New Orleans, 8.1 per cent (8).

Comment. A reasonable figure for the incidence of perforation among patients with peptic ulcer rests somewhere between 3 and 13 per cent.

The incidence of perforation is not large when compared to the total hospital admissions; a variation between hospitals also occurs here. A better idea of the general incidence is obtained by grouping a large number of reports. In 1,193,916 hospital admissions collected by De Bakey (8), there were 7,859 cases of peptic ulcer, or 0.685 per cent (685 per 100,000). In 1,478,445 hospital admissions, there were 1290 cases of perforation, or 0.087 per cent (87 per 100,000) or, 13.2 per cent of the cases of peptic ulcer were perforated.

Incidence of Recurrent Perforations

The incidence of *recurrent perforations* is apparently low. In Tidy's (10) relatively large series, recurrent perforations occur in 0.6 per cent of all admissions for gastric ulcer and in 1 per cent of all admissions for duodenal ulcer; they occur in 4 per cent of all patients admitted with perforated gastric ulcer and 5 per cent of all admitted with perforated duodenal ulcer. Cohn (11) reported an incidence of 1.3 per cent in 300 cases in California and Wakeley (12) 2 per cent in 100 cases in England. In a collected series of 6538 cases of perforation, De Bakey (8) found an incidence of 1.1 per cent of reperforations.

In some cases, the reperforation has occurred at a former site identified by the presence of suture material; in other cases, the perforation occurred at a new site (8). Some patients have had and survived as many as five perforations (8). Its recurrence at the site of an old suture may indicate that the suture was a contributory cause.

It is of interest to note that the mortality on reperforation is significantly less than on perforation, probably due to immunization by the first perforation (Table 44).

Table 44

REPERFORATIONS OF PEPTIC ULCER

	No.	*Per Cent*
Mortality		
Perforated	..	27.0
Reperforated	..	9.0
Total		
Perforations*	4813	..
Reperforations*	33	0.69
Perforations†	6538	..
Reperforations†	72	1.1

* Lysaght and Williams (60).
† De Bakey (8).

The perforation of two ulcers simultaneously, *double perforation*, rarely occurs (8, 13). Nevertheless, more than one ulcer, *multiple ulcers*, is found in from 18 to 40 per cent of perforated cases (7, 14).

INCREASING INCIDENCE

There is no doubt that the number of *recognized cases* of perforated peptic ulcer admitted to hospitals has increased since 1910 (8). There is a question, however, regarding whether the number of perforations have increased out of proportion to the increase in the number of recognized cases of peptic ulcer. De Bakey (8) presents some evidence that such is the case. Some 20 other authors interpret their data similarly, but further study of this question is required before it can be concluded that perforated ulcer has increased out of proportion to the increase in the incidence of peptic ulcer.

RELATIVE INCIDENCE OF PERFORATION OF GASTRIC AND DUODENAL ULCER

The literature is very confused regarding the relative incidence of perforations of gastric and duodenal ulcer. Many cases do not come to

autopsy, and, as has been pointed out by several authors, a pylo
or prepyloric ulcer may be called a duodenal ulcer at operati
caution is exercised (15). The pyloric vein may be covered with
the difference in the palpatory thickness of the duodenum ov
inflammation of the duodenal wall. For example, Fallis (16) in 1
records 44 juxtapyloric perforations and 33 duodenal, and then
most of the 44 pyloric ulcers were probably duodenal in location.

Further, the relative incidence of gastric and duodenal u
changed during the last 100 years, and the incidence of ulcer at
sites may vary among different populations (17).

The autopsy data collected during similar periods agree fai
At Leeds, England, in 180 autopsies in which gastric ulcer was
36 per cent had perforated, and in 313 autopsies in which duoden
was present, 56 per cent had perforated (2). At Cook County H
Chicago, a charity hospital, in 55 autopsies in which gastric u
present, 44 per cent or 24 had perforated, and in 65 autopsies
duodenal ulcer was present, 68 per cent or 43 had perforated
another series of autopsies at Cook County Hospital, Chicago, th
152 gastric and 188 duodenal perforations, yielding an autopsy
was 1.2 D.U.: 1.0 G.U. (18). Both groups of data suggest that a
ulcer may be more prone to perforate than a gastric ulcer. This question
further study in which the perforations at autopsy should be
along with those admitted to surgery and in relation to the total
admission for gastric and duodenal ulcer.

The *extensive clinical literature* on this question varies very
even during the same period of observation. In different hos
London prior to 1942, the ratio of perforations of the duoden
stomach varied from 1:9 to 9:1 (19). Gilmour and Saint (20) in N
England, reported in 1933 that only 10 per cent of perforations
their hospital were gastric. In 1930, Williams and Walsh (15) in
reported four duodenal perforations to one gastric perforation. E
Ebeling (21) in Philadelphia reported four duodenal to one gas
foration in 1934. Yudin in Russia in 1937 observed 10 duodena
gastric perforation. At Cook County Hospital, Chicago, between
1938 inclusive, 700 perforated ulcers were seen, of which 50.5 per c
duodenal and 49.5 per cent were gastric (22); this ratio was clos
observed at autopsy during the same period (5). In 1940 Meyer
New York City reported one duodenal to 3.5 gastric perforati
cases 104). In 1943 in England, Stewart and Winser (19) rep
duodenal to 1.6 gastric perforations in 897 cases. In 1944, in N
England, Raw (24) reported 12 (282 cases) duodenal to one
gastric perforation in 306 patients, the same as 10 years previously

e hospital. De Bakey (8), in 11,305 collected cases, found that cent (4400 cases) were classified as gastric and 51.2 per cent as l (5791 cases) and 9.8 per cent as pyloric (1114 cases). More ports on the perforation of gastric and duodenal ulcer show that lence is approximately equal (25–27).

data, like autopsy data, do not provide a reliable idea of what ge of gastric or duodenal ulcer patients perforate.

945, Tidy (10) in England reported one duodenal to 1.2 gastric ions in 445 cases. Tidy's data, which are most impressive, also at although the actual number of gastric ulcer patients, both with hout perforation, was greater than the number of duodenal ulcer with and without perforation, the duodenal ulcers tended to e more readily (Table 45).

Table 45

AGE DISTRIBUTION OF PEPTIC ULCERS AND PERFORATIONS FROM 1922 TO 1937 AT ST. THOMAS HOSPITAL, LONDON

Age	*Males*						
	Total Admissions		*Ratio G.U.:D.U.*	*Perforations*			
				Perforation		*Per Cent Admissions*	
	G.U.	*D.U.*		*G.U.*	*D.U.*	*G.U.*	*D.U.*
0–20	4	5	0.8:1	1	3		
20–30	143	156	0.9:1	41	36	29	23
30–40	382	262	1.5:1	55	47	14.4	18
40–50	500	304	1.6:1	75	56	15	18
50–60	375	213	1.8:1	43	41	11.5	20
60–	176	85	2.1:1	25	22	14	26
Total	1580	1025	1.5:1	240	205	15.2	20

Perforations form 17 per cent of male and 4.5 per cent of female dmissions, a difference which is statistically significant.

MENT. Though the question of the relative incidence of perforation c and duodenal ulcer is not settled by these data, all pertinent and autopsy data show that *duodenal ulcer is somewhat more prone te.*

ust be recognized, however, that there are regional and hospital ces in the clinical and postmortem data on the incidence of gastric

and duodenal ulcer which indicate a difference in environmental ulc genic factors (28). This accounts to a large extent for the variable resu

Relation of Occupation to Incidence of Perforation

The clinical data presented by Tidy from St. Thomas Hospita charity hospital in London, do not differ materially from the autopsy clinical data from Cook County Hospital, Chicago, also a charity hosp Tidy presents evidence which indicates, if it does not prove, that ga ulcer occurs more frequently in skilled and unskilled manual workers t in professional workers; among the latter, more duodenal than ga ulcers occur. The data are presented in Table 46.

Table 46

Indicating That a Social Factor Is Concerned in the Relative Incidenc Mortality from Gastric and Duodenal Ulcer

Standardized Mortality Ratios, England*

Social Class	*Males—Age 20–65 yrs.*				*Married Wo Age 35–6 1930–32 G.U. and D*
	1921–23		*1930–32†*		
	G.U.	*D.U.*	*G.U.*	*D.U.*	
I. Professional	72	126	55	101	53
II. Semiprofessional and managerial	87	109	76	106	98
III. Skilled workers	96	91	99	99	99
IV. Semiskilled	105	93	109	93	99
V. Unskilled workers	127	113	127	107	118

* From Tidy (10).

† Note for 1930 to 1932 G.U. is 55 per cent of the expected rate of Clas among members of Class I. D.U. is essentially the same in all classes.

In 1467 collected cases of perforation, De Bakey (8) found that 5 cent were laborers and 18.2 per cent followed sedentary occupat The largest number of cases come from charity hospitals where ga ulcers are seen more frequently than duodenal. Laborers may de less attention to the care of their ulcer. This should be taken into sideration in the interpretation of statistics.

Factor of Sex

The old German and English literature, which showed a gr incidence of gastric than duodenal ulcer, and a higher incidence of g ulcer in women than men, records that perforation was about twi common in the female. This literature also showed that 1 perforati

c ulcer occurs in the male for 1.8 in the female, and that 2.7 perfora-
of duodenal ulcer occur in the male for 1 in the female (17).
recent times, all are agreed that perforation occurs more frequently
male whether it be gastric or duodenal. This is more true of the
al than the autopsy reports. In an autopsy report from Leeds, Eng-
the ratio was 1.3 M:1.0 F for gastric perforations and 1.7 M:1.0 F
uodenal perforations (2). At Cook County Hospital, Chicago, the
for all perforations was 44 M:1 F. This marked difference is not
nted for by the fact that males constitute about 60 per cent of the
ssions. In Seattle, Washington, the sex ratio of fatal perforations was
:1 F. Among surgical reports, 14,339 cases have been collected (8),

Table 47

FEMALE CASES OF PERFORATED ULCER AS A PERCENTAGE OF THE TOTAL CASES IN RECORDED SERIES*

Period of Years	*Author*	*No. of Cases*	*Female Percentage of Total*
1857	1	230	64
1903	2	361	63
1915	3	244	43
1925	4	180	30
1925	4	551	25
1925	5	1500	25
1925–40	4, 5, 6, 7, 8, 9, 10, 11	2581	6
1934	4, 12	2630	5
1941	13	1055	7

* From Stewart & Winser (19).

1. Brinton (61).
2. Brünner (40).
3. Schoemaker (62).
4. Schwarz (63).
5. Bager (9).
6. Jennings (32).
7. Sallick (64).
8. Shelley (65).
9. Gilmour & Saint (20).
10. Zukschwerdt (66).
11. Hinton (67).
12. Eliason & Ebeling (21).
13. Stewart & Winser (19).

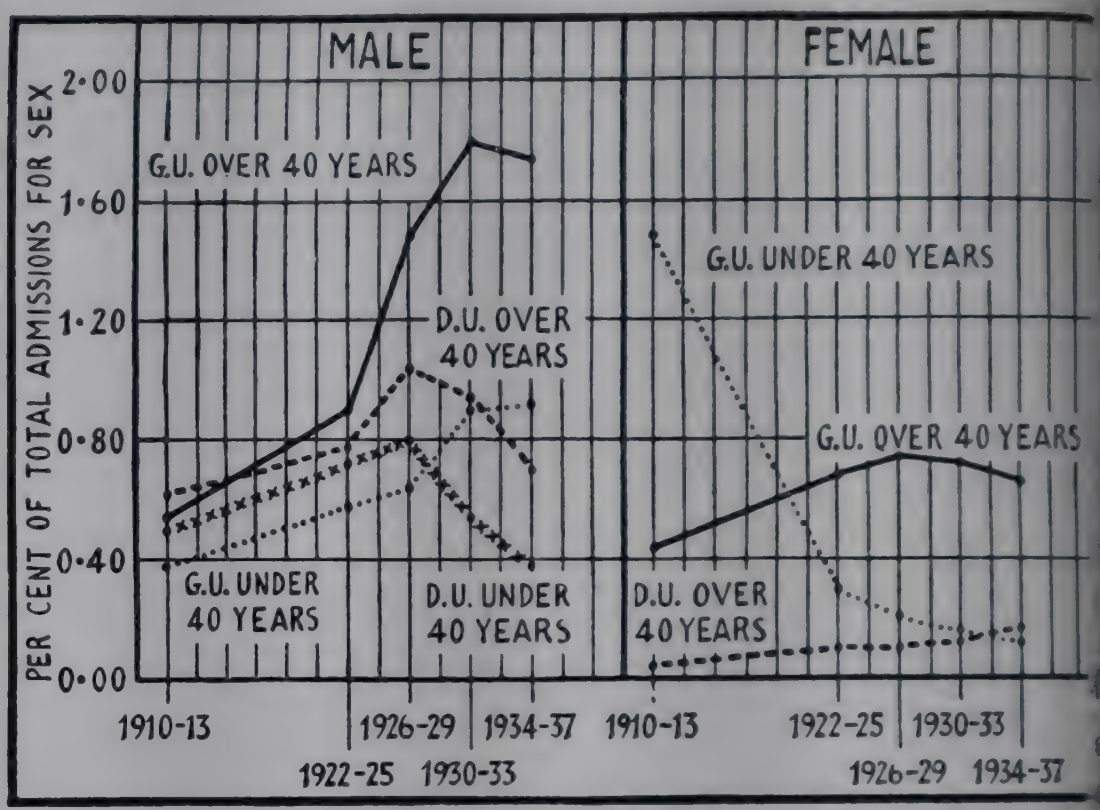


FIG. 96. Showing changes in admissions with time at St. Thomas Hospital, Lon
(Courtesy, Tidy: *Brit. M. J.*, **1**:319, 1945.)

in which the percentage of males was 92.2 per cent. (See also refs. 15, 22, 28–31.)

Table 47 shows that the percentage of perforations in females markedly decreased since 1903. Jennings (32) has emphasized how yo women have almost ceased to ulcerate and perforate. Tidy presents g evidence showing that the decrease in perforations in women under 4 London, as is true everywhere, is due to a decrease in incidence of u and not to a change in liability to perforate. In this group, the fa admissions, perforations, and deaths was practically over in 1932, whe it formed the largest group until 1914 (Fig. 96). He points out that removal of some external etiologic factor or factors must have accou for this change. This change in the sex incidence of perforation is n more impressive than the change in autopsy statistics and hospital ad sions for nonperforated peptic ulcer.

FACTOR OF AGE

Perforation of a peptic ulcer may occur at any age (33), even *in* (34). Nevertheless, it is uncommon below the age of 20 and above the of 70.

The age distribution of 6875 cases is shown in Table 48. Seventy-t per cent of the cases of perforation occur between 20 and 50 years of

ure 97 indicates how the data from different sources vary, though it is ibtful whether the difference is really significant. When such differes do occur, the number of duodenal and gastric ulcers in the populan must be considered, as, for example, in Stewart and Winser's group irve IV, figure 97), where there were a large number of gastric ulcers 4 G.U. and 343 D.U.).

Table 48

SHOWING THE AGE INCIDENCE OF PERFORATED PEPTIC ULCERS*

Age	*6,875 Cases (Gastric and Duodenal)*	*2,429 Cases*	
		Gastric	*Duodenal*
0–9	0.07%		
10–19	3.7	4.9%	7.2%
20–29	23.9	15.5	28.9
30–39	27.5	21.8	29.1
40–49	22.3	28.3	17.2
50–59	15.0	22.1	11.7
60–69	5.8	9.3	5.9
70–79	1.6		
80+	0.06		

* De Bakey (8).

Perforation of duodenal ulcer tends to occur in a younger age group. 2429 cases, it was found that 65 per cent of duodenal perforations curred in patients under 40 years of age and 60 per cent of gastric rforations occurred in patients above 40 years of age (Table 48).

FACTOR OF RACE

The view once held that perforated peptic ulcer occurs less frequently negroes has been disproved (8). The same seems to be true of the inese, since the incidence of perforation at the Peiping Union Medical ollege Hospital was found to be 10.2 per cent (43). When any significant fferences appear to have been established, environmental factors should carefully excluded before attributing such a difference to a racial factor 5–38).

SEASONAL INCIDENCE OF PERFORATIONS

Mortality data from the U.S. Census show a statistically significant eak in mortality in November and December, and another insignificant

peak in April (p. 722); August shows the lowest mortality. These data d not differentiate between perforation, hemorrhage, and stenosis as a caus of death.

A study of perforations in London, England, revealed a statistically significant peak in December; August was the lowest (39). Several author have reported a fall peak (40–42). Yudin in Russia gives the monthl occurrence of 273 cases of perforation, in which May and October repre sent the peak months. De Bakey (8) collected 2334 cases of perforatio

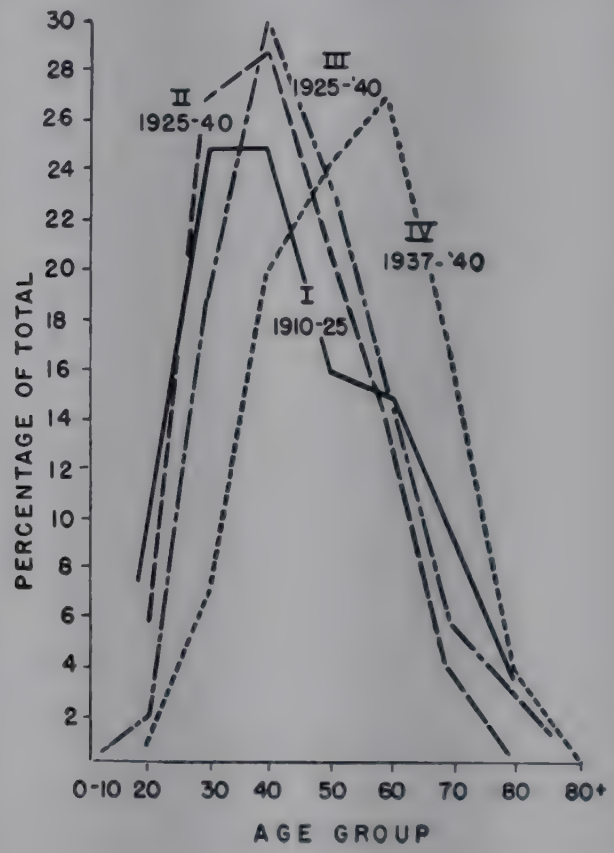


FIG. 97. Incidence of perforated ulcer by decades in surgical series: *I*, Sweden, 1910–25 (1089 cases); *II*, Europe, 1925–40 (672 cases); *III*, United States, 1925–40 (1678 cases); *IV*, London, England, 1937–40 (832 cases). (Courtesy, Stewart & Winser: *Lancet*, **1**:259, 1942.)

with the following results: spring, 28.6 per cent; summer, 22.4 per cen fall, 23.9 per cent; winter, 25.0 per cent. All reports from the Northe hemisphere, except that of Shawan (30) from Detroit, find the lowe incidence in summer.

It is probably unwise to pool data by seasons rather than months, a it is unwise to pool data from many parts of the world according to seaso since environmental factors vary so widely. Methods similar to those us by the London group (39) to show that the December peak was significa should be applied to data obtained on various populations.

Factor of Heavy Air Raids

In London, England, during World War II, it was clearly established t during a period of heavy air raids the incidence of perforations was nificantly increased (39). Duodenal and gastric perforations were ally increased in males and the incidence of perforations in the female s increased but not significantly so. Some factor operated to cause an rease in the incidence of perforation. Fear and anxiety were suspected).

This observation in England is supported by the report from Sweden) that perforations increased 35 per cent in 1942 during the most trying iod of the war.

Other Factors Which May Predispose to Perforation: Time of Day, Meals, Exertion, and Rest

Most perforations occur during the daytime; this is supported by all evidence. Bager (9) in Sweden found a peak between 4 and 6 P.M. idin (29) in Russia found a peak between 11 A.M. and 11 P.M. Brünner) observed that 50 per cent of ulcers which perforate do so within 2.5 urs after eating the principal meal. In a study of 700 cases, McNealey d Howser (22) found that the perforation occurred within three hours er a meal in 47 per cent of cases, between three and six hours after a al in 38 per cent, and six to 20 hours after a meal in 15 per cent. In a ies of 1672 perforations collected by De Bakey (8), only 34 (2 per cent) curred during a barium meal examination. It is clear from these and er data in the literature (8) that simple distension of the stomach not an important factor.

External pressure has been observed apparently to cause perforation. a small series of cases, external pressure is presumed to have caused rforation in from 2 to 11 per cent of cases (68). In 1260 cases collected De Bakey (8), only 50 or 4 per cent were believed to be due to external essure or trauma.

In 700 cases, perforation occurred in 3.3 per cent during straining, in .6 per cent during moderate exertion, in 51.1 per cent while at rest but vake, in 12.7 per cent while asleep, and in 6.3 per cent while eating or inking (22). Since so many perforations occur at rest, or while asleep or ider management in a hospital, pressure exerted on the gastric contents om outside the abdomen cannot be an important factor (Table 49).

Concomitant Hemorrhage and Perforation

It has been said that "bleeding ulcers rarely perforate and perforating cers rarely bleed." This impression was studied carefully by Winters and

Egan (18). They found hemorrhage present in 13 per cent of perforation of the stomach and 8 per cent of the duodenum. Further, 10 per cent or 3 of their 361 patients who perforated gave a history of hemorrhage. Massiv hemorrhage occurred in 14 of the 36 one to seven days before the per foration and in nine, eight to 15 days before. The remainder had bled fo varying periods. Fourteen per cent gave no history of symptoms prior t perforation. This is questioned by White and Patterson (45), who clai that a careful history will usually reveal symptoms of an ulcer. Oth

Table 49

SHOWING ACTIVITIES AT TIME OF PERFORATIONS
100 CASES

	*No. Patients**	*Per Cent of Those Recorded**	*No. Patients†*	*Per Cent‡*
At work	27	36.4	24	26.6
While straining	..	..	..	3.3
Resting at home	20	27.0	..	51.1
In bed at home	7	9.5	19	12.7
In hospital	6	8.1	8	..
Walking	6	8.1	..	..
After eating or drinking water	4	5.4	14	6.3
Driving auto	2	2.7	..	..
After taking laxative	..	..	9	..
Hunting	1	1.4	..	..
Drinking beer	1	1.4	..	..
Total recorded	74	100.0	74	..
Unrecorded	26	..	26	..
Total	100	..	100	..

* Fallis (16).
† Moore & Hendricks (46).
‡ De Bakey (8).

articles in the literature report an incidence of from 1.5 to 18 per ce (average 8 per cent) of concomitant hemorrhage and perforation (21 In 2525 cases of perforated ulcer collected by De Bakey (8), associat hemorrhage occurred in 155 or 6.1 per cent. More recently, this associ tion has been observed in as many as 26.9 per cent (26) and 20 per ce of patients (46).

Hemorrhage is more likely to be associated with perforation abo the age of 50 years (18).

Anterior Location of Most Perforated Ulcers

As indicated previously (p. 512), most frank perforations occur on the rior wall of the duodenum and of the prepyloric region and near the r curvature, the majority occurring within one inch on either side e pyloric sphincter (16, 31). In 200 autopsies on chronic gastric ulcer, 29.5 per cent) had perforated anteriorly; five (2.5 per cent), poste- ly; and four (2.0 per cent), in both directions (2). In 180 duodenal rs, 73 (70 per cent) of 104 anteriorly located duodenal ulcers had orated, and only 10 (13 per cent) of 76 posteriorly located ulcers had orated. In a series of 1523 perforated ulcers, only 33 or 2.16 per cent e located posteriorly (8).

This principle of the anterior perforation of peptic ulcer is explained the fact that anteriorly located ulcers have much less opportunity of oming attached to or based upon an adjacent structure.

Gross Appearance of the Perforating Ulcer

There are two types. The first and most common is the *soft lesion*, which evoid of indurated edges, and tends to be small in size and not adherent neighboring structures. The second is the *hard or callous lesion*, which ds to be a large, deep lesion frequently adherent to surrounding ctures. The size of the perforation varies from 1 mm. up to 2 cm. (8).

Minor Acute Perforation with Spontaneous Closure, or "Subacute" Perforation, or Forme Fruste Perforation

A minor acute perforation is one in which the perforation is relatively ll and the symptoms are relatively mild and quickly abate. This type alled "gedeckte perforation" in Germany and "perforation fermée et ée" in France. Relatively little leakage of gastric or duodenal contents urs, though air, which shifts with a change in posture, is found under diaphragm in the standing position.

In the group of cases observed by Singer and Vaughan (47), two thirds the patients had been sent to the medical ward with the diagnosis of otic ulcer.

There is no good report in the literature providing adequate data the incidence of this type of perforation. During a period in which 12 es of classical perforated peptic ulcer were admitted to the Cook unty Hospital, Chicago, 14 cases of minor acute perforation were nd (47). This would indicate that minor acute perforations are proba- as frequent as major acute perforations.

The recognition of all of these cases and their operation would result

in a low surgical mortality and be a factor influencing the surgical mo tality, just as would occur if all patients with manifest hemorrhage we operated upon.

These minor perforations lead to the formation of adhesions and coul cause an intractable type of distress and yield poorly or not at all medical therapy.

The expression "chronic perforation" is sometimes used to indica those cases in which some adjacent organ or tissue forms the base of th ulcer.

Relation of Previous Ulcer History to Perforation

A previous ulcer history is clearly obtained in 85 per cent of perfor tions (8). In the remainder, there was no previous dyspepsia or only such a short duration as to make no particular impression on the patien

A good study of the relation of the duration of the ulcer history to th likelihood of perforation, like that made by Stolte for hemorrhage, h not been made. The literature would indicate, however, that during th first year of the disease, the rate is somewhat higher, like hemorrhage, an after that the incidence of perforation becomes stable (10).

Perforation of Anastomotic Ulcer

Eight hundred and seventy-two cases of anastomotic ulcer have bee collected from the literature in which the number of cases of perforat ulcer is provided (2, 48–55). In this group of 872 cases of anastomotic ulce 133 or 15.3 per cent had perforated. Though this is within the ran reported in the literature for the incidence of perforation of peptic ulce it is obviously too high. Like perforation of peptic ulcer, the true in dence probably resides somewhere between 3 and 13 per cent. It cann be stated that the tendency of anastomotic ulcer to perforate is a greater or less than the tendency for gastric or duodenal ulcer to perfora Jejunal ulcers perforate; marginal ulcers rarely perforate.

Only two authors provide mortality statistics. Wright (48), in a co lective inquiry, had 17 deaths in 60 perforations (28 per cent), which much lower than that reported by Paterson. Paterson (51) collected cases up to 1909 and found that 14 out of 19 cases of perforated anas motic ulcers, or 74 per cent, died. This was in the early days after gastr enterostomy when such ulcers were not recognized and the patient w practically moribund on hospital admission.

Cause of Perforation of a Peptic Ulcer

It is reasonable to assume that any gastric or duodenal ulcer m perforate and that those which perforate do so because of the excessi operation of those factors which cause the ulcer. The factors favori

oration, then, would be: (a) an excessive secretion of acid; (b) an ease in mechanical traumatic factors; and (c) a dimunition in local e resistance to digestion and in healing potential.

t is known from animal experimentation (p. 217) that excessive acid tion may produce a perforated duodenal or gastric ulcer. When an sion ulcer is made in the stomach, the administration of histamine will e it to extend or to perforate in some but not all animals (56–58). l, by penetrating into the wall of blood vessels, will cause an end- ritis and thrombosis, and in this way decrease the healing potential the resistance to digestion.

The instillation of acid or the administration of histamine in beeswax e more ulcers and perforations of the duodenum than the stomach. s agrees with the greater tendency of duodenal ulcer to perforate. vever, in those populations where gastric ulcer and perforated gastric r is as prevalent as perforated duodenal ulcer, some additional factor as increased intragastric pressure or rough and irritating food would required to explain the high incidence of gastric perforation. Before essive acid alone could account for perforation, it would have to be onstrated experimentally or clinically that with an equal distribution lcers between the stomach and duodenum, as in London (p. 613), an ease in acid alone would cause perforation at both sites to increase.

Table 50

SHOWING LACK OF CORRELATION BETWEEN ACIDITY OF GASTRIC CONTENTS AND COMPLICATIONS OF PEPTIC ULCER*

ree HCl nits	*Number of Patients*	*Per Cent with No Complication*	*Per Cent with Obstruction*	*Per Cent with Hemorrhage*	*Per Cent with Perforation*	*Per Cent with Hour Glass Deformity*	*Per Cent with Jejunal Ulcer*
–20	128	53.9	13.2	22.6	3.9	1.5	4.6
–40	224	46.9	22.3	22.3	3.1	2.2	3.1
–60	290	47.2	20.6	22.4	3.1	2.7	3.7
–80	214	47.6	18.7	25.7	3.2	0.4	4.2
+	138	46.3	19.5	24.6	5.0		4.3

* From Emery and Monroe (1).

There is little clinical evidence bearing on the relation of acid secretion perforation. The data of Emery and Monroe (1) (Table 50), which are e most extensive, show that the incidence of perforation is not correlated th the acidity of the gastric contents as determined by a test-meal. The ount of secretion as well as its acidity is important, and this is not vealed by a test-meal. The fact that perforations occur in the newborn,

where acid secretion is at a low ebb under normal conditions, would against acid-pepsin being the prime causative factor in all cases of pe tion and in favor of a local causative factor in some cases.

External pressure on the gastric contents is not an important According to Corlette (59), this is because an increase in intra-abd pressure is immediately transmitted to the gastric contents, and do exert a strain on an ulcer.

The ingestion of a meal, because of receptive relaxation of the st and an associated relaxation of the abdominal wall (Von Merings' r does not cause an increase in intra-abdominal pressure. Peristaltic a causes a rise in intragastric pressure and tends to be more forceful t the end of gastric digestion and in the presence of pyloric obstructi some persons, anxiety increases intragastric pressure.

The greater tendency for duodenal than gastric ulcer to perfo ascribed to the thinner duodenal wall. The greater incidence of perfo in males for both gastric and duodenal ulcer may be explained greater acid secretion of males and their tendency to devote less at to dietary hygiene. The best explanation of the phenomenal decr incidence of perforated gastric ulcer in females under 40 is the disa ance of tight lacing.

The observation that duodenal ulcer has approximately the incidence in all social classes but gastric ulcer has a lower inc in professional groups (Table 46) indicates that both groups are e to factors which stimulate the secretion of excessive acid but the sional group may expose his stomach to fewer mechanical and chemical irritants. The December increase in perforations is to be ex since that is probably the most frequent period for recurrences o The only gastric change known to occur in the stomach in fall and is a change in the quantity and viscosity of the mucin obtained fr mucosa.

The failure of the incidence of perforations in the female to i significantly during the period of heavy air raids may have been du few cases of duodenal and gastric ulcer. Before the heavy raids, th of male perforations to female was 14:1 and during the raids 13 The total increase during the raids was small though significant increase noted in females may have been too small to be significa

Summary

It appears that in the last two decades between 3 and 13 per ce ulcer patients perforate. The incidence of reperforation is approx 1 per cent. The incidence of recognized perforation has increas 1910, but whether it has increased faster than the incidence of rec

ulcer is equivocal. Duodenal ulcer is more prone than gastric ulcer
orate, but the incidence of perforated duodenal ulcer as compared
orated gastric ulcer varies widely with different hospital popula-
The data suggest that perforated gastric ulcer predominates in
s and that perforated duodenal ulcer predominates in professional
nprofessional groups. Perforated peptic ulcer occurs at least nine
more frequently in the male. Prior to 1911, the incidence was
t in the female under 40 years of age, and this was due to a high
ce of perforated gastric ulcer. Most perforations occur between 20
years of age; most occur in the fourth decade though in some series
ak occurs in the fifth decade. It has not been demonstrated that
ffects the incidence of perforation; environmental factors appear
important. In certain populations, December is significantly the
nonth for perforations and August the lowest. Other data on this
on are confusing because they have not been analyzed statistically.
nal and hospital differences in the same region occur in the incidence
foration. Such factors as the relative incidence of gastric and duo-
ulcer, occupation, sex, age, time of year, and the state of peace or
s well as the reputation of a hospital as regards gastric surgery
cantly affect the incidence of perforations.

emorrhage and perforation occur concomitantly in approximately
cent of cases of perforated peptic ulcer. At least 95 per cent of the
which perforate do so anteriorly. Both acute and chronic ulcers
rate.

ost ulcers perforate during the waking hours, within six hours after
st meal, and during moderate exertion or rest. External pressure
aining is associated with perforation in approximately 4 per cent
cases.

would appear that acid is essential for the perforation of an ulcer
he evidence does not indicate that an excessive secretion of acid
ntial.

Hemorrhage

he literature varies considerably regarding the incidence and mor-
from hemorrhage in peptic ulcer. This should be expected in view
many factors concerned, one of which is the definition of the term
plied to peptic ulcer.

Definition

eryone is agreed regarding the meaning of *occult blood* as detected by
cal methods. There is no confusion regarding the meaning of
st bleeding, which refers to the presence of red blood in the vomitus
atemesis) or to black tarry stools (melena).

A loss of 60 cc. of blood will yield a dark stool on a milk an diet and 80 to 100 cc. a black stool on a general diet (69); even form a clot in the gastric contents. This is not a significant l *per se;* yet, such a hemorrhage is sometimes referred to as "g "massive" hemorrhage (70). In some articles, "gross" is used in sense as manifest or visible evidence of bleeding. On the othe "massive bleeding" is frequently used to indicate severe bleeding degree of blood loss which *per se* threatens life as evidenced by weakness, fainting, or shock. Unfortunately, the appearance of the toms depends to a significant extent on the acuteness of the hem

Some authors have attempted to classify the degree of hemor (a) mild or minor, (b) moderate, and (c) severe. A severe hem could be of two types: one, "gradual" being characterized by a anemia, 3 Gm. of hemoglobin per 100 cc. of blood or less; and, t "sudden" or "acute" being characterized by prostration and an of up to 10 Gm. of hemoglobin per 100 cc. of blood. The consensu who define "severe hemorrhage" requires (a) prostration or the of bed rest, (b) a red cell count of 2.0 to 3.0 million or less, (c) globin of 3 to 7 Gm., and (d) a pulse rate of 120 to 140.

Table 51

SHOWING VARIATIONS IN CLASSIFICATION OF DEGREE OF HEMORRHA IN PEPTIC ULCER

Author	*No. Cases Manifest Hemorrhage*	*Mild*		*Moderate*		
		No. Cases	*Per Cent*	*No. Cases*	*Per Cent*	*No. Ca*
Mossberg (110)	318	82	26	..	..	23
Kirsner & Palmer (70)	232	42	18.2	65	28.3	12
Allen & Benedict (105)	628	252	40.1	176	28.0	23
Petsopopoulos (111)	433	15	3.7	138	31.9	28
Baker* (72)	497	214	43.0	191	38.3	9
Mattison (112)	736	71	9.6	463	63.1	2
Total	2526	594	23.5	1033	40.9	8

* Hemoglobin below 30 per cent for "severe" and above 60 per cent for

The data in Table 51 illustrate the variation encountered attempt is made to grade the degree of hemorrhage. It will be n in the 2526 cases approximately one third were graded as severe, be predicted in the presence of three grades when no exact crite used or are available. Until this problem of diagnosis of the

hage is solved to the satisfaction of all, it would appear to be best are mortality and incidence on the basis of manifest hemorrhage han on the basis of "massive" or "severe" hemorrhage.

tic Ulcer as a Cause of Manifest Hemorrhage from the Upper Gastrointestinal Tract

ther factor complicating the present question of evaluating the e regarding bleeding peptic ulcer is that hematemesis and/or may occur in many diseases of the upper alimentary tract. Many lata dealing with this subject have been collected in Table 52. In ses of manifest upper alimentary bleeding, approximately 72 per ange 60 to 90 per cent) were due to peptic ulcer.

Table 52

Showing the Relative Frequency of Gastrointestinal Bleeding Due to Various Causes*

Source of Bleeding	*Total Cases*	*Per Cent*	*Range (%)*
Ulcer	3310	71.7	59–90
Cancer	478	10.3	2–17
is of Liver	204	4.4	1–14
s	84	1.8	..
Anemia	49	1.0	..
ystitis	28	0.6	..
Causes or Miscellaneous	172	3.9	..
rmined or Unknown	250	5.4	..
rix Esophageal Disease	5	..	..
Hernia	5	..	..
f Stomach	2	..	..
s of Stomach Other than Ca or Polyps	4	..	..
or Metabolic Disease	4	..	..
Dyscrasia	2	..	..
al Poisons	2	..	..
Thrombosis	1	..	..
Gastric Causes	3	..	..
culum of Duodenum	1	..	..
s of Duodenum	1	..	..
notic Ulcer†	†	..	..
erous Disease of Intestine	8	..	..
al Ileitis	1	..	..
	4614	..	..

ferences 89, 90, 98, 106, 113–120.
cluded with peptic ulcer.

Hematemesis and Melena in Hemorrhage from Gastric and Duodenal Ulcer

Another factor which may have been a source of error in the literature was the thought that hematemesis indicated the existence gastric rather than duodenal ulcer. Alsted (71) cites a total of 1881 of bleeding peptic ulcer from the literature prior to 1910 in which matemesis occurred in 1199 and melena alone in 682, or 36 per cent remarks that melena may have been unnoticed; however, in 1026 of bleeding peptic ulcer from the more recent literature, melena a appeared in 332, or 32 per cent (Table 53). It is also clear from the mo literature that hematemesis may occur without melena, even in duo and anastomotic ulcer, and that melena alone occurs more frequent duodenal than gastric ulcer.

Table 53, Part A

Showing the Incidence of Hematemesis and Melena in Gastric and Duodenal Ulcer

Author	*Gastric Ulcer*			*Duodenal Ulcer*			*Anastomotic U*	
	Hemat.	*Melena*	*Both*	*Hemat.*	*Melena*	*Both*	*Hemat.*	*Melena*
Franzen (121)	112	45	*	51	48	..	4	1
Graham et al (74)	35	13	11	69	42	23	3	2
Goldman (96)	45	47	21	82	137	55	..	..
Andresen (122)	...	..	..	12	28	80	..	..
Allen (75)	..	..	..	84	142	145	..	..
Total	192	105	32	298	397	303	7	3

* Not given.

Part B

Melena with and without Hematemesis*

Degree of Hemorrhage	*With Vomiting*		*Without Vomiting*	
	Cases	*Per Cent*	*Cases*	*Per Cent*
Mild†	187	43.0	27	50.0
Moderate	172	39.5	19	35.0
Severe†	84	17.5	8	15.0

* Baker (72).

† Hemoglobin below 30 per cent in the "severe" and above 60 per cent in the mild cases.

matemesis obviously indicates the acuteness and perhaps to the xtent the severity of the hemorrhage more than the site of the bleed- er. Baker (72) has recently emphasized this point (Table 53, Part B). h the severely bleeding ulcer patient usually vomits as well as blood, death may occur from a bleeding duodenal ulcer without and from bleeding gastric ulcer without hematemesis.

Frequency of Hemorrhage in Peptic Ulcer

matemesis and melena were regarded as the most certain symptoms tic ulcer prior to the introduction of roentgenography. For reasons above and others to be noted later, the data on the frequency of rhage in peptic ulcer are subject to considerable error. As most rs point out, a considerable portion of patients without a previous y of peptic ulcer are admitted to a hospital because of upper ali- ary tract hemorrhage and then on x-ray examination two or three later show no evidence of a peptic ulcer.

ostmortem Statistics. Postmortem statistics show that death due to eding peptic ulcer is relatively rare. Bleeding ulcer was the cause of in 0.37 per cent of 6302 autopsies reported by Conybeare (73) and 1 per cent of 9000 autopsies reported by Stewart (2). Hemorrhage is, theless, an important cause of death in peptic ulcer in some autopsy ts. For example, it was a cause of death in 67, or 55.8 per cent, of ases in Chicago in which peptic ulcer was the primary disease and .6 per cent of 339 cases dying with peptic ulcer. On the other hand, s the cause of death of only 38 or 7.3 per cent of cases of peptic ulcer ng to autopsy in Leeds, England (2). The autopsy rate for patients g of hemorrhage with a peptic ulcer history may have been low.

dmissions to Hospitals for Bleeding Peptic Ulcer. The fre- cy of hemorrhage from peptic ulcer as a cause of admission to a tal is also relatively rare. In a total of 247,725 admissions, 3641 had c ulcer and 884 a severe hemorrhage. Thus, the admission rate for c ulcer was 1.4 per cent and for severe hemorrhage from peptic ulcer per cent, or one fourth of the admissions for peptic ulcer (74–79). incidence of 25 per cent checks with the clinical incidence derived able 56.

linical Incidence and Mortality of Bleeding Peptic Ulcer. A of the clinical incidence and mortality of bleeding ulcer reveals al interesting points related to the natural history of peptic ulcer. rior to 1912, before the introduction of roentgenography and when ing was so important diagnostically, the incidence of manifest ing ranged from 30 to 80 per cent (Table 54). Since then, a com- on of the data in the articles which present the larger number of

Table 52

OLDER LITERATURE PROVIDING DATA ON THE INCIDENCE OF HE... IN PEPTIC ULCER*

Author	Period	Per Cent of Incidence	Author	Per...
Brinton	1852	29	Greenough & Jones	1888
Müller	1860	29	Harsted	1890
Lebert	1878	80	Kemp	1906
With	1877–81	30	Friedenwald	1912
Osler	1898	50	Kemp	1913

* Alsted (71).

cases shows that manifest hemorrhage occurs in an average ... of peptic ulcer patients admitted to hospitals (Tables 55 a... United States, the British Isles, Germany, and Scandinavia... corresponds to that used by Balfour (58), who states that 2...

Table 55

SUMMARY OF INCIDENCE OF MANIFEST HEMORRHAGE AND MORTALITY IN PEPTIC ULCER*

Peptic Ulcer Cases	23,942
Manifest Hemorrhage	5,984
Per Cent	25, range 10 to 50
Peptic Ulcer Cases	23,422
Hemorrhage Cases	5,193 (22 per cent)
Unadjusted Deaths	444
Per Cent	8.5, range 1 to 25
Adjusted deaths	399
Per Cent	7.5, range 1 to 2...
Per Cent of P.U. Cases	1.6, range 1 to 5
Hemorrhage Cases	14,973
Unadjusted Deaths	8 per cent
Adjusted Deaths	7 per cent

* See Tables 56, 57.

ulcer patients are found to bleed if followed for an averag... This checks well with the figure observed by Emery and M... 28.7 per cent in 1435 patients followed for an average of 1.9

o 45 per cent in the different reports is not surprising when one e variable factors involved and the definition of what consti morrhage from a peptic ulcer.

Table 30

THE CLINICAL INCIDENCE OF MANIFEST HEMORRHAGE IN PATIENTS WITH PEPTIC ULCER SINCE 1913†

...or	Period	Cases P.U.	Hemorrhage Cases		Geographic Location
			No. Cases	Per Cent	
2)	1910–17	1631	736	45.1	Sweden
23)	1912–20	500	95	19.0	Battle Creek, U.S.A.
)	1915–25	426	101	23.7	New York
...tfall (78)	1921–30	1662	120	7.2*	London
7)	1913–31	1266	105	8.0*	Sweden
0)	1922–31	1032	318	30.8	Sweden
...rse (1)	1913–32	1435	384	26.7	Boston
	1923–32	1436	136	9.4*	Boston
...ling (21)	1924–34	638	143	22.2	Philadelphia
)	1928–34	990	349	38.0	San Francisco
	1919–35	1852	433	23.4	Berlin
4)	1925–35	495	200	39.8	Berlin
e (125)	1920–36	1554	429	27.9	London
	1927–37	545	155	28.2	San Francisco
Cole (94)	1919–39	1076	208	19.0	Seattle
	1899–1939	1832	887	48.4	Amsterdam
artin (126)	1926–38	343	62	18.1	Philadelphia
l. (74)	1929–38	434	193	44.5	Glasgow
Hardy (127)	Prior to '38	430	131	30.4	New Orleans
...irner (70)	1929–38	2156	230	10.6	Chicago
	1931–40	456	182	40.0	U.S.A.
r (83)	1930–40	1145	267	22.4	Stockholm
	1945	714	120	17.0	London
	...	23943	5964	25.0	Range 10 to 45 per cent

nt hemorrhage on the same patient, when recorded, is omitted to prevent e patient twice.

nearly as possible, include gastric and duodenal ulcers only.

dence of acute perforation was found to be 13 per cent (p is one half of the incidence of manifest hemorrhage. If the spontaneously closing perforations is as high as acute perfora-

Table 57

CLINICAL MORTALITY FROM HEMORRHAGE FROM GASTRIC AND DUODENAL ULCER SINCE 1910

Author	*Period*	*No. P.U. Cases*	*No. Hem. Cases*	*Mortality*						
				Over-all		*Corrected*		*P.U. Cases*		
				No. Deaths	*Per Cent*	*No. Deaths*	*Per Cent of Hem. Cases*	*No. Deaths*	*Per Cent of Ulcer Cases*	
Mattison* (112)	1910–17	1631	736	23	6.9	14	3.1	14	0.86	Sweden
Manheim† (91)	1915–25	426	101	9	9.0	4	4.2	4	0.9	New York
Burger & Hartfall‡ (78)	1921–30	1662	120†	31	25.8†	18	15.3	18	1.1	London
Enocksson‡ (77)	1913–31	1266	105†	14	13.3†	12	11.3	12	0.9	Sweden
Mossberg (110)	1922–31	1032	318	28	9.0	28	9.0	28	2.7	Sweden
Chiesman‡ (128)	1925–31	1812	191	46	24.0	46	24.0	46	2.5	England
Emery & Monroe (1)	1913–32	1435	384	20	5.2	20	5.2	20	1.3	Boston
Allen‡ (89)	1923–32	1436	136	19	14.5†	19	14.5	19	1.3	Boston
Ehason & Ebeling (21)	1924–34	638	143	4	2.7	4	2.7	4	0.6	Philadelphia
Goldman (96)	1928–34	890	349	56	15.0	39	11.1	39	4.4	San Francisco
Umber (41)	1919–35	1852	433	41	9.5	41	9.5	41	2.2	Berlin
Kalk (124)	1925–35	495	200	16	8.0	16	8.0	16	3.2	Berlin
Hurst & Ryle (125)										
(Private Cases)	1920–36	1183	347	7	2.0	6	1.7	6	0.5	England
(Hospital)	1919–35	371	82	4	4.8	3	3.6	3	0.8	London
Kruse (95)	1927–37	545	155	29	18.7	29	18.7	29	5.3	San Francisco
Blackford & Cole (94)	1919–39	1076	208	8	3.8	8	3.8	8	0.7	Seattle
Pfeiffer & Martin (126)	1926–38	343	62	8	12.9	8	12.9	8	2.3	Philadelphia
Graham et al. (74)	1929–38	434	193	22	11.4	22	11.4	22	5.0	Glasgow
Browne & McHardy (127)	'38	430	131	7	5.3	5	3.8	5	1.2	New Orleans
Kirsner & Palmer (70)	1929–39	2150	230	8	3.5	5	1.3	5	0.4	Chicago
Bohrer (79)	1931–40	456	182	14	7.8	14	7.8	14	3.0	U.S.A.
Ihre & Müller (85)	1930–40	1145	267	11	4.1	10	3.7	10	0.8	Stockholm
Baker (72)	1945	714	120	19	15.7	19	15.7	19	2.7	London
Total	..	23422	5193§	444	8.5	390	7.5	390	1.6	..

Eleven reports range from 1.7 to 7.8 per cent (corrected).
Ten reports range from 8.0 to 15.7 per cent (corrected). Corrected mortality excludes deaths not attributable to hemorrhage.
* [illegible] mortality in severe bleeding 6.9 per cent; 14 deaths in 202 cases.

as indicated by Singer and Vaughan (p. 553), then the incidence of oration and hemorrhage is approximately the same.

The incidence of manifest hemorrhage may actually be higher than er cent when special attention is given to the history. Stolte (81) found to be true in a selected group of patients which were studied intensively he incidence of hemorrhage.

Clinical Mortality of Bleeding Peptic Ulcer. It might be thought the clinical mortality of bleeding ulcer would provide a less variable x of the incidence of this complication of the disease. Data on this t have been collected in Tables 57 and 58. It will be noted in Table 55 in a group of 23,422 ulcer patients, 5193 or 22 per cent bled. Of those bled, 444 or 8.5 per cent died due to exsanguination or due to some rcurrent disease which aggravated the effect of the hemorrhage or ch the hemorrhage aggravated. In Table 58 it is seen that 7.7 per cent 780 bleeding ulcer patients died. Combining the two groups, 8 per cent 4,973 bleeding ulcer patients died. The range for different reports is to 26 per cent.

In most instances, the high mortality was due to the selection of vere" cases. This is supported by the fact that the range for deaths to hemorrhage in all peptic ulcer patients admitted is only 0.9 to per cent, average 1.6 per cent. It is obvious that statistical reports on eding ulcer would vary less when the criterion is either the presence of tarry stool" or bright blood in the vomitus than when one tries to grade degree of hemorrhage by methods which are admittedly inaccurate.

The elder gastroenterologists used manifest bleeding as the criterion hemorrhage from peptic ulcer (Table 58) and they obtained a rela- ly low mortality from bleeding ulcer, like those who report low rtalities today. Those with low mortalities may not draw so many ients from a population that enters a hospital as a last resort.

Relation of Mortality to Hemoglobin and Erythrocyte Concentration

There are a number of reports in the literature in which either hemo- bin or erythrocyte values are given and related to the mortality of patients. The data are too heterogeneous in most instances to evaluate. owever, an attempt to do this has been made in Table 59, where it will noted, as might be anticipated, that more deaths occurred when the moglobin or erythrocyte level was lower than 50 per cent of normal an when above. However, none of these articles state when the hemo- bin or erythrocyte estimation was made in relation to the onset of the od loss. Rafsky (82) has used the lowest value for hemoglobin and thrócyte count obtained during the patient's early stage of hospitaliza-

Table 58

MORTALITY FROM HEMORRHAGE FROM GASTRIC AND DUODENAL ULC

Author	*Period*	*No. Hem. Cases*	*Mortality*				*Le*
			Over-all		*Operated*		
			No. Deaths	*Per Cent*	*No. Deaths*	*Per Cent*	
Bulmer (119)	1902–31	578	62	10.7	62	10.7	England
Frostad (129)	1916–32	382	35	9.4			Norway
Cullinan & Price† (130)	1925–29	105	19	18.1	15	14.8	England
Christiansen (100)	1923–32	289	23	7.9	20	7.8	Denmark
Hellier (90)	1926–32	171	24	14.0	23	13.5	England
Davies & Nevin (131)	1924–33	391	84	21.5	84	21.5	England
Aitken (132)	1929–33	255	27	11.0	22	8.9	England
Rischel (4)	1931–34	220	2	0.9	2	0.9	Denmark
Venndt (102)	1925–30	178	14	7.9	12	6.7	Sweden
"	1931–35	288	7	2.4	6	2.1	Sweden
Reschke (101)	1934–35	1000	95	9.5	95	9.5	Berlin
Crohn & Lerner (133)	1927–37	236	20	8.5	20	8.5	New Y
Hesser (134, 135)	1929–37	406	16	3.9	16	3.9	Sweden
Motzfeldt (136)	1927–32	113	5	4.2	5	4.2	
"	1932–37	154	5	3.2	5	3.2	Sweden
Jankelson & Segal (137)	'38	200	21	10.5	21	10.5	Boston
Andresen (122)	'39	173	4	2.3	4	2.3	New Y
Marshall & Kiefer (138)	'39	108	5	4.4	5	4.4	Lakes C
Römcke (139)	1935–39	209	6	3.0	6	3.0	Sweden
Clemmesen & Lund (140)	'39	273	20	7.3	7	2.7	Sweden
Franzen (121)	1928–33	211	14	6.6	14	6.6	Sweden
"	1934–40	339	10	2.9	10	2.9	Sweden
Woldman (142)	'41	144	3	2.1	3	2.1	Clevela
Thorstad (143)	1931–41	284	21	7.4	21	7.4	Detroit
Rafsky & Weingarten (82)	1927–41	342	36	10.5	18	5.2	New Y
Schiff (120)	'43	160	11	6.8	8	5.1	
Thompson et al. (113)	'44	111	24	21.6	24	21.6	Los An
Rasberry & Miller (141)	'44	72	4	5.3	3	4.4	Philad
Baker (72)	1940–45	576	77	13.4	68	12.0	Londo
Eads (116)	'46	102	2	2.0	2	2.0	
Bohmansson (144)	1929–38	306	28	9.1	28	9.1	Sweden
	1939–45	253	12	5.1	12	5.1	Sweden
Wilkinson & Tracey (145)	'46	140	5	3.5	5	3.5	Lakes
Meulengracht (106)	1931–46	1031	26	2.5	16	1.5	Denma
Totals	..	9780	757	7.7	688	6.7	
Lenhartz‡§		201	9	5.0	—	—	Germa
Ewald§	—	188	8	4.8	—	—	Germa
Wurzberg§		320	19	5.9	11	11	Germa
Hawkins§		56	4	6.7	—	11	Englan
		1243	57	5.0	—	—	

* From those including which did not provide the total number of peptic ulcers.
† Duo. cases with hemorrhage presented.
‡ Lenhartz favoured prompt feeding.
§ Cited by Paterson [146].

seen within four or six hours, a patient that has suffered an acute hage may have a relatively normal hemoglobin or erythrocyte Twenty-four or 48 hours are required for the restoration of fluid On the other hand, the patient may have had anemia due to blood bloss and the loss of a little blood would be serious. Burger rtfall (78) report that in patients hospitalized for hemorrhage, the ance of bleeding after being placed on bed rest was of more value in is than the estimation of hemoglobin level.

re can be no doubt that the degree of blood loss determines life or

Table 59

ATION OF MORTALITY TO HEMOGLOBIN OR ERYTHROCYTE ESTIMATION

Author	*Below 50 Per Cent Hb (8 Gm.) or Below 3 Mil R B C*			*Above 50 Per Cent Hb or Above 3 Mil R B C*		
	No. Cases	*No. Deaths*	*Per Cent*	*No. Cases*	*No. Deaths*	*Per Cent*
& Hartfall (78)	63	12	19	40	5	13
& Palmer (70)	97	7	8	133	0	0
20)	121	11	9	39	0	0
t al. (98)	121	19	16	99	5	5
	402	49	12.2	311	10	3.2

Rafsky (*Per. Gastroenterol.*, **11**:93. 1944) for his method of grading.

Table 60

MORTALITY IN RELATION TO RECENT RECURRENCES AND RELAPSES UNDER TREATMENT IN A HOSPITAL

Author	*Per Cent Mortality*	
	Without Relapses	*Continued or Recurrent Bleeding*
Babey & Hurst (147)	0.0	27
Burger & Hartfall (78)	8.5	33
Chiesman (128)	1.6	74
Davies & Nevin (131)	9.8	53
Holman (148)	6.4	46
Cullinan & Price (130)	17.4	63
Baker (72)	4.2	31

death, and the need of the patient for a blood transfusion. Yet, the he globin level alone without a circulating blood volume may not indi the extent of blood loss and whether the patient is still bleeding or whe the bleeding will recur in a short time.

Relation of Recent Recurrences of Hemorrhage to Mortality

Every author agrees that continued or recurrent bleeding before particularly after entering the hospital portends a fatal outcome. Data presented in Table 60 which adequately demonstrate this to be true.

Relation of Number of Nonrecent Hemorrhages Suffered by Patient to Mortality

It has been contended, *pro and con*, that the first hemorrhage is m likely to be fatal than subsequent hemorrhages. The evidence on this p is collected in Table 61. Except in those instances where the data have b collected for three or more hemorrhages, it would appear that the hemorrhage is more likely to prove lethal. When the data from var sources are grouped to cancel errors of random sampling, a signific difference is not found. In fact, when an adequate number of cases included in one group, a significant difference is not found (see Table Part A). (It will be indicated later that the older a patient is when develops an ulcer, the more likely he is to die of hemorrhage if the u bleeds.)

This consideration raises several questions. What per cent of her rhages in patients admitted to hospitals represent a recurrent hemorrh Is a patient who has had a hemorrhage more prone to hemorrhage a than one who has not hemorrhaged? What is the relation of the dura of peptic ulcer disease to the onset of hemorrhage?

Incidence of Recurrent Hemorrhage in Patients Admitte to a Hospital for Hemorrhage

As shown in Table 62, 1453 or 33 per cent of 4447 patients adm for bleeding ulcer had bled before. The range is from 11 to 57 per cen

Is a Patient with Bleeding Ulcer More Prone to Bleed tha One without a Bleeding Ulcer?

Jordan and Kiefer (83) present follow-up data which show that blee ulcer patients relapse by bleeding more frequently than nonbleeding u patients (Table 63). These data show a significant difference over a year period. The rate of relapses of patients with an uncomplicated complicated peptic ulcer forms a straight line or is proportional with

Mortality in Relation to the Number of Previous Hemorrhages

Author	Hemorrhages											
	1st Hem.			2nd Hem.			3rd Hem.			4th Hem.		
	No. Cases	No. Deaths	Per Cent	No. Cases	No. Deaths	Per Cent	No. Cases	No. Deaths	Per Cent	No. Cases	No. Deaths	Per Cent
Part A												
Hesser (134)	406	16	3.9	122	4	3.3	..	..	..	..	..	..
Sullens, et al (98)	140	12	9.2	56	9	15.8	8	3	37.5	26	3	1.2
Ralsky & Weingarten (82)	283	23	8.8	84	10	11.8	25	2	8.0	16	1	6.3
Christiansen (100)	203	18	8.9	86	5	5.9	..	..	..	..	..	..
Total A	1032	69	6.7	348	28	8.0	33	5	15.1	42	4	9.9

Part B	1st Hem.			All Subsequent Hem. Observed		
Babey & Hurst (147)	371	4	1.1	160	4	2.4
Burger & Hartfall (78)	59	5	8.5	58	26	44.0
Wilkinson & Tracey (145)	70	1	1.4	23	3	13.0
Jones (109)	126	10	8.0	58	12	2.1
Baker (72)	443	61	13.8	123	14	11.4
Jankelson & Segal (137)	179	20	11.2	21	1	5.0
Total B	1248	101	8.1	443	60	13.8

Part C							Totals					
							1st Hem.			Subsequent Hem.		
Crohn (149)	101	9	..	..	0							
Goldman (96)	209	6	..	..	30							
Allen & Benedict (105)	138	12	..	..	7		No. Cases	No. Deaths	Per Cent	No. Cases	No. Deaths	Per Cent
						A + B	2280	170	7.4	866	97	11.3
Total C	448	27	6.0	..	37	A + B + C	2728	197	7.2			

Part D								
Thorstad (143)	..	18	..	..	3		No. Deaths in 1st Hem.	No. Deaths in Subseq. Hem.
Kirsner & Palmer (70)	..	5	..	..	3			
Total D	..	23	..	..	6		220	151

or the duration of the disease, which is a very significant observation from the viewpoint of the biology of ulcer disease.

Relation of the Duration of Peptic Ulcer Disease to the Onset of Hemorrhage

Hemorrhage as a First Symptom. It is quite well known that hemorrhage may occur as the first symptom of the presence of an ulcer. A crater may be found which has caused no pain ("silent ulcer"). The incidence

Table 62

Per Cent of Patients with Hemorrhage from Gastric and Duodenal Ulcer Who Were Relapsing due to Hemorrhage

Author	*No. Hem. Cases*	*No. with Relapse*	*Per Cent with Relapse*
Hesser (134)	406	122	30
Mossberg (110)	295	85	30
Rischel (4)	192	69	35
Franzen (121)	550	148	27
Babey & Hurst (147)	371	106	29
Burger & Hartfall (78)	137	78	57
Schiff (120)	160	81	50
Jones, F. A. (109)	126	58	46
Christiansen (100)	289	86	30
Allen (75)	119	48	40
Mattison (112)	736	233	32
Rafsky & Weingarten (82)	283	125	44
Baker (72)	443	123	27
Jankelson & Segal (137)	200	21	11
Wilkinson & Tracey (145)	140	66	55
Total	4447	1453	33

Average, 33 per cent recurrences; range 11 to 57 per cent.

of hemorrhage as a first symptom of peptic ulcer ranges from 3 to 50 per cent. The average of 16.2 per cent (Table 64) of hemorrhages as the first symptom compares well with 14 per cent of perforations (p. 554) as the first symptom of an ulcer.

Some have ascribed these findings to the taking of a poor history, which may be true in part. However, if 10 per cent of all ulcers are "silent," it is reasonable to believe that an ulcer leading to hemorrhage or perforation may be silent in 10 per cent of cases. In this connection, Kalk (84) found a higher incidence of hemorrhage as a first symptom in gastric

than in duodenal ulcer, which agrees with the reasonable view that a duodenal ulcer causes distress more readily than a gastric ulcer.

AVERAGE DURATION OF SYMPTOMS BEFORE A HEMORRHAGE. Most ulcers before they bleed cause distress for a long period. This is supported by a

Table 63

RECURRENCE RATE IN BLEEDING AND NONBLEEDING PEPTIC ULCER PATIENTS*

	No. Pts.	Recurrences by Years									
		1		2		3		4		5	
		No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
A. Uncomplicated†	148	22	15	30	20	37	25	41	28	52	35
B. 1 Hemorrhage	42	8	18	11	25	15	36	16	38	18	42
C. 2+ "	19	7	38	12	62	14	74	15	79	15	79
D. 2+ "	13			7	54						
C + D	32			13	41.0						

At 2 Yr.	Relapse	No Relapses	Total
B. 1 hem.	11	31	42
C + D. 2+	13	19	32
Total	24	50	74

$\chi^2 = 1.6$; not significant.

At 5 Yr.	Relapse	No Relapses	Total
B. 1 hem.	18	24	42
C. 2+	15	4	19
Total	33	28	61

$\chi^2 = 8.1$; significant.

Showing that bleeding ulcer patients relapse by bleeding more frequently than non-bleeding ulcer patients.

* From Jordan and Kiefer (83).

† Recurrence not due to hemorrhage or obstruction.

large literature, which, however, is presented too heterogenously to tabulate. For example, Alsted (71) found that 65 per cent of patients who bleed have had ulcer symptoms for two years or longer. Burger and Hartfall (78) found that 50 per cent have had symptoms from one to five years and Kirsner and Palmer (70) for one to 10 years before the first hemorrhage.

Ihre and Müller (85) found that the average duration of symptoms due

Table 64

HEMORRHAGE AS A FIRST SYMPTOM OF PEPTIC ULCER

Author	*No. Cases Hem.*	*No Cases with Hem. as 1st Symptom*	*Per Cent*
Rafsky & Weingarten (82)	283	43	15.2
Andresen (122)	120	17	14.1
Kalk (84, 124) Gastric	154	10	6.4
Duodenal	46	1	2.2
Rischel (4)	180	54	2.9
Kirsner & Palmer (70)	230	22	9.6
Woldman (142)	144	29	20.0
Wilkinson & Tracey (145)	140	70	50.0
Burger & Hartfall (78)	137	9	6.8
Eads (116)	129	14	10.8
Schiff (120)	115	12	10.0
Total	1678	281	16.2

Table 65

SHOWING THE RELATION OF DURATION OF PEPTIC ULCER DISEASE TO THE OCCURRENCE OF HEMORRHAGE IN 333 PEPTIC ULCER PATIENTS FOLLOWED FROM THE START OF ULCER DISTRESS TO 1940*

Duration of Complaints	*No. Cases*	*No. Hem.*	*Per Cent Hem.*
1 Yr.	320	65	20.3
2 Yrs.	303	76	25.1
3 "	295	89	30.2
4 "	280	97	34.6
5 "	270	100	37.0
6 "	257	106	41.2
10 "	246	126	51.2
20 "	221	150	67.9
30 "	187	160	85.6

* Stolte (81).

to gastric ulcer before hemorrhage was 4.5 ± 0.84 years; the same figure for duodenal ulcer was 4.7 ± 0.52 years. The difference is not significant. Kalk's (84) data also show no difference in the average time of onset of bleeding from a gastric or duodenal ulcer after the onset of ulcer symptoms.

Stolte (86) found no sex difference in the frequency of the relapses of

Table 66

FREQUENCY OF BLEEDING IN SUCCESSIVE DECADES OF ULCER DISEASE IN 320 PATIENTS*

Part A	*Decade of Ulcer Disease*						*Average*
	1st	*2nd*	*3rd*	*4th*	*5th*	*6th*	
Total Ulcer Years	2112	838	319	135	52	10	3466
No. of Hemorrhages	178	45	16	8	4	1	252
Percentage	8.4	5.4	5	5.9	7.7†	10†	13.7

Part B	*Decade of Ulcer Disease*						*Average*
	1st	*2nd*	*3rd*	*4th*	*5th*	*6th*	
Females							
Total Ulcer Years	517	259	156	97	41	10	1080
No. of Hemorrhages	47	11	5	6	4	1	74
Percentage	9.1	4.3	3.2	6.2	9.8	10	6.8
Males							
Total Ulcer Years	1595	579	163	38	11	..	2386
No. of Hemorrhages	131	34	11	2	..	..	178
Percentage	8.2	5.9	6.7	5.3	..	..	7.5

Part C	*Frequency Relative to Age in 320 Patients*							
	0–20	*20–30*	*30–40*	*40–50*	*50–60*	*60–70*	*70–80*	*80+*
Years of Disease	215	716	1030	859	511	233	71	4
No. of Hemorrhages	9	20	60	62	47	36	17	1
Percentage	4.2	2.8	5.8	7.2	9.2	15.4	24.0	25.0

* Stolte (81, 86).

† Not statistically significant, due perhaps to too few cases. Three hundred and thirty-three patients had 252 hemorrhages in 3466 years; an average of approximately 1 every 14 years.

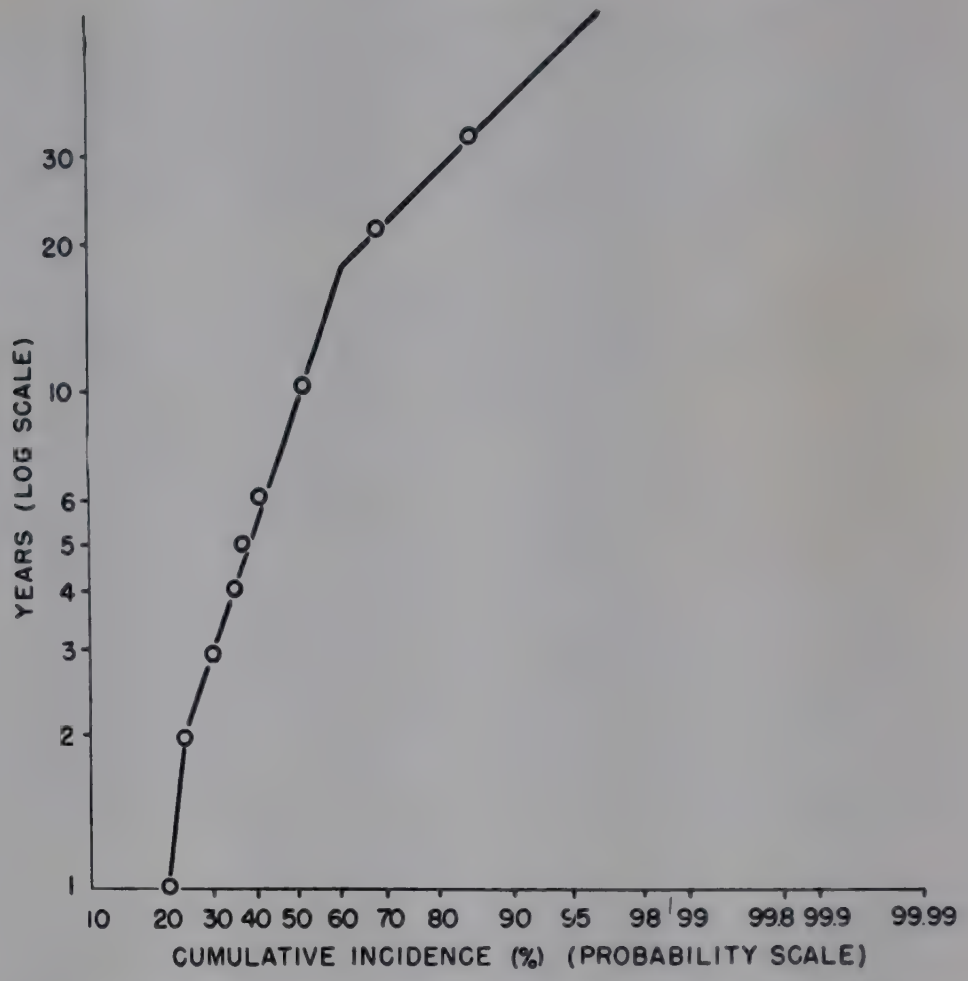


FIG. 98. The cumulative incidence of a history of hemorrhage in patients with peptic ulcer in relation to the years of duration of the disease.

bleeding ulcer; 52, or 64 per cent, of 81 females and 134, or 53.2 per cent, of 252 males had one or more manifest hemorrhages.

THE LONGER THE DURATION OF ULCER DISEASE, THE GREATER THE CHANCE OF HEMORRHAGE

Data submitted by Stolte (81) clearly show that the longer the duration of ulcer disease, the greater the chance that the patient has had a manifest hemorrhage. He personally examined the histories of 333 ulcer patients for manifest hemorrhage from the onset of their ulcer symptoms. His findings are shown in Tables 65 and 66 and graphed on a probability scale in Figure 98. Except for a greater tendency to bleed in the first year and a lesser tendency after the 10th year of the disease, the frequency of bleeding is directly related to the duration of the disease.

These data of Stolte would indicate that approximately 90 per cent of ulcer patients would develop one hemorrhage provided they lived for 40 years after the onset of ulcer disease. Jordan and Kiefer (83) have also found a slightly greater tendency to hemorrhage in the first year, after

which their data yields a straight line graph for the five years during which they followed their patients.

This observation of Jordan and Kiefer and of Stolte is obviously a significant contribution toward establishing the existence of a basic susceptibility to recurrences of the disease. It would certainly take a followup for more than five or even 10 years to disprove the conclusion that "once a potential ulcer patient, always a potential ulcer patient." This observation does not annul the possibility that some ulcer patients may enter a remission and remain there for 30 or more years in the absence of environmental factors which predispose to a recurrence. Emery and Monroe (1) and others have seen three or more patients who have had a remission of more than 20 years. Neither does the observation argue against the existence of a group of ulcer patients with a special tendency to bleed.

Does a Group of Peptic Ulcer Patients with a Special Tendency to Bleed Exist?

Jordan and Kiefer (83) found that when the recurrence rate in patients with uncomplicated peptic ulcer is graphed, a straight line results (Table 63). The same is true, as indicated above, of recurrences in bleeding ulcer patients; however, the rate of recurrences is significantly greater in patients with the complication of hemorrhage, especially if it has occurred two or more times. Apparently, the occurrence of hemorrhage in a patient indicates the existence of a greater susceptibility to ulcer disease. Though the authors state that most of the recurrences were associated with a "gross" hemorrhage, they do not provide data to determine whether the group is significantly prone to hemorrhage. Clinically, one gains the impression that some patients are very prone to bleed, but adequate data are not available to establish the truth of this impression.

Relation of Site of Ulcer to Clinical Incidence of Hemorrhage

The relative clinical incidence of hemorrhage from gastric and from duodenal ulcer (Table 67) since 1913 varies significantly among different populations. This is evident in the most recent reports, which are shown in Table 65.

Since 1912 in the United States, more bleeding ulcers are clinically diagnosed as duodenal in location, the ratio being 4 D.U. to 1 G.U. This is the reverse of the report of Greenough and Joslin (87) from the Massachusetts General Hospital in 1899.

In Scandinavia since 1915, the incidence of hemorrhage from duodenal ulcer is about as high as in the United States. But in Germany, the

Table 67

RELATIVE CLINICAL INCIDENCE OF HEMORRHAGE FROM GASTRIC AND FROM DUODENAL ULCER SINCE 1913

Author	*Period*	*Total Cases G.U. + D.U.*	*G.U. No. Cases*	*D.U. No. Cases*	*Geographic*
Emery & Monroe (1)	1913–32	1382	215	1167	Boston
Manheim (91)	1915–25	101	53	48	New York
Allen (89)	1923–32	136	42	94	Boston
Eliason & Ebeling (21)	1924–34	143	36	107	Philadelphia
Miller & Elsom (150)*	1918–38	55	5	50	Philadelphi
Pfeiffer & Martin (126)*	1926–38	59	15	44	Philadelphi
Rivers & Wilbur (118)	1927–28	421	65	356	Mayo Cli
Kruse (95)	1927–37	155	42	113	San Franc
Crohn & Lerner (133)	1927–37	250	54	196	New York
Rafsky & Weingarten (82)	1927–41	342	55	287	New York
Kirsner & Palmer (70)	1929–39	192	17	175	Chicago
Andresen (122)	Prior to '39	94	16	78	New York
Browne & McHardy (127)	Prior to '39	124	36	88	New Orlea
Woldman (142)	1935–39	121	22	99	Cleveland
Bohrer (79)†	1911–41	660	184	476	U.S.A. Q
Thorstad (143)	1931–41	263	90	173	Detroit
Eads (116)	1941–45	102	8	94	Philadelphi
Schiff (120)	1937–43	150	33	117	Cincinnati
Thompson et al. (113)	1911–46	79	25	54	Los Angel
Total (U.S.A.)	..	4829	1013	3816	
Hurst & Ryle (125)	1920–36	347	79	268	Private Pr. Hospital A
" " "	1919–35	76	54	22	London
Burger & Hartfall (78)	1921–30	120	95	25	London
Bulmer (119)	1926–31	72	58	14	Birmingha England
Hellier (90)	1926–32	171	120	51	Leeds, En
Graham et al. (74)	1929–38	193	59	134	Glasgow
Baker (72)	1940–45	212	100	112	London
Total (Great Britain)	..	1191	565	626	
Christiansen (100)	1923–32	54	18	36	Copenhag
Rischel (4)	1931–35	111	26	85	Copenhag
Total (Denmark)		165	44	121	
Hesser (134, 135)	1929–37	82	27	55	Sweden
Franzen (121)	1928–40	169	84	85	Lund, Sw
Ihre & Müller (85)	1930–40	254	80	174	Stockholm
Total (Sweden)		505	191	314	
Kalk (124)	1925–35	200	154	46	Berlin
Petsopopoulos (111)	1931–35	433	323	110	Berlin
Total (Germany)	..	633	477	156	

* Massive hemorrhage.
† Results of questionnaire from surgeons.

Author	Period	Total No. Cases P.U.	Gastric Ulcer					Duodenal Ulcer				
			Total No. Cases	No. Cases Hem.	Per Cent Hem.	No. Hem. Deaths	Per Cent Hem. Deaths	Total No. Cases	No. Cases Hem.	Per Cent Hem.	No. Hem. Deaths	Per Cent Hem. Deaths
Hurst & Ryle (125)	1920–36	1183	241	79	32.8	4	5.0	942	268	28.4	3	1.1
" (Hosp. Cases)* (2)	1919–35	358	191	54	27.0	4	8.0	167	22	13.1	0	0
Allen (75)	1923–32	1436	434	42	9.6	6	14.0	1002	94	9.3	13	14.0
Eliason & Ebeling (21)	1924–34	638	92†	36	39.1	3	8.3	546	107	19.5	1	0.9
Kalk (84)	1925–35	495	253	154	60.8	12	4.7	242	46	18.0	4	1.6
Total	..	4110	1211	365	30.1	29	7.9	2899	537	18.5	18	3.3
Manheim (91)	1915–25	426	180	53	29.5	..	..	246	48	19.5	..	..
Burger & Hartfall* (78)	1921–30	1662	888	95	10.6	..	..	774	25	3.2	..	..
Kruse (95)	1927–37	545	146	42	28.0	..	..	399	113	28.0	..	..
Ihre & Müller (85)	1930–40	1145	257	80	31.1	..	..	888	174	19.6	..	..
Total	..	3778	1471	270	18.4	..	..	2307	459	19.9	..	..
Total above	..	4110	1211	365	30.1	..	..	2899	537	18.5	..	..
Grand total	..	7888	2682	635	23.7	..	7.9	5206	996	19.1	..	3.3

7.9 − 3.3 = 4.6; this difference is significant.
30.1 − 18.5 = 11.6; " " " "
23.7 − 19.1 = 4.6; " " " "

* Only severe cases entered by author.
† Data on 91 additional cases were not available.

incidence of hemorrhage from gastric ulcer was as high in
thirties as it was from duodenal ulcer in the United States. The
situation in England is most interesting. In the hospitals in L
some outside London, hemorrhage from gastric ulcer is more fre
from duodenal ulcer; whereas in private practice and som
outside London bleeding from duodenal ulcer is more prev
matter of occupation is probably involved, as indicated in the
of perforation (p. 546). Just what the etiologic difference in oc
or social classes may be is ripe for investigation. Environmental
undoubtedly involved.

The Relation of Site of Ulcer to Bleeding Tenden
Mortality from Hemorrhage

It is commonly stated in the literature that gastric ulcer ren
more frequently and fatally than duodenal ulcer. The data i
Table 68 show that the statement is correct. According to
23.7 per cent of gastric ulcers and 19.1 per cent of duodenal u

Table 69

Relative Clinical Mortality from Hemorrhage from Gas
and Duodenal Ulcer since 1919

Author	Period	Gastric Ulcer			Duodenal Ulcer		
		No. Cases Hem.	No. Deaths	Per Cent Deaths	No. Cases Hem.	No. Deaths	Per Cent Deaths
Hurst & Ryle (125)	1919–35	54	4	8.0	22	0	0
Hurst & Ryle (125)	1920–36	79	4	5.0	268	3	1.1
Allen & Benedict (105)	1923–32	42	6	14.0	94	13	14.0
Elmore & Ebeling (21)	1924–34	36	3	8.3	107	1	0.9
Kalk (84)	1925–35	154	12	4.7	69	4	1.6
Hellier (90)	1926–32	120	18	15.1	51	6	11.8
Kraus (95)	1927–37	42	12	28.0	113	31	28.0
Crohn & Lerner (130)	1927–37	39	4	10.3	147	10	6.1
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Rudisy & Weingarten (82)	1927–41	58	14	24.1	298	21	7.2
Thorstad (143)	1931–41	90	8	8.9	173	9	5.2
Bohrer (79)*	Prior to '41	700	44	22.9	455	86	18.8
Schiff (128)	1937–45	32	5	15.5	197	3	0.9
Baker (7)	1940–45	100	36	36.0	112	16	14.3
Totals		1546	111	14.4	2156	113	8.9

14.4 − 8.9 = 7.9; the difference is significant.

* Results from a questionnaire made out by surgeons.

SHOWING CLINICAL INCIDENCE AND MORTALITY FROM HEMORRHAGE FROM PEPTIC ULCER IN MEN AND WOMEN

Author	Period	No. Cases P.U.	Men					Women				
			No. Cases P.U.	No. Cases Hem.	Per Cent Hem.	No. Deaths	Per Cent Deaths	No. Cases P.U.	No. Cases Hem.	Per Cent Hem.	No. Deaths	Per Cent Deaths
Enockson (77)	1913–21	1266	805	68	8.4	8	11.8	461	37	8.0	6	16.2
Chesman (128)	1925–31	1812	1410	137	9.7	37	27.0	402	54	13.4	8	15.6
Baker (72)	1945	714	549	80	14.7	12	15.0	165	40	23.6	7	17.5
Total		3792	2764	285	10.4	57	20.0	1028	131	12.7	21	16.0
Stolte (86)	1899–36	1499	992	399	40.3	..	..	507	302	59.6	..	..
..	1936–39	333	252	184	55.9	..	..	81	52	64.2	..	..
Alsted (71)	1926–36	8684	5713	788	13.8	..	..	2971	471	15.8	..	..
Ihre & Müller (85)	1930–40	1145	811	184	22.6	..	..	334	70	21.0	..	..
Total		11661	7768	1555	20.0	..	20.0	3893	795	20.4	..	16.0

20.0 − 16.0 = 4.0; this is not significant.

These data show that there is no sex difference in the tendency to bleed from a peptic ulcer.

The difference is not marked; yet, it is a statistically significant differen
The data in Tables 68 and 69 show that bleeding from a gastric is abo
twice as hazardous as from a duodenal ulcer. The difference in t
mortality rate for gastric and duodenal ulcer in the smaller (Table
and larger (Table 69) groups of cases is striking. In the larger series,

Table 71

CLINICAL MORTALITY FROM HEMORRHAGE FROM PEPTIC ULCER IN MEN AND WOMEN SINCE 1913*

Author	*Period*	*Men*			*Women*			*Cou*
		No. Cases Hem.	*No. Deaths*	*Per Cent Deaths*	*No. Cases Hem.*	*No. Deaths*	*Per Cent Deaths*	
Enocksson (77)	..	68	8	11.8	37	6	16.2	Swec
Burger & Hartfall (78)	1921–30	95	27	28.5	42	4	9.0	Engl
Chiesman (128)	1925–31	137	37	27.0	54	8	15.6	Engl
Bulmer (119)	1926–31	80	12	15.0	31	3	9.7	Engl
Christiansen (100)	1923–32	211	15	7.1	78	8	10.3	Den
Hellier (90)	1926–32	146	18	13.0	56	6	12.5	Engl
Venndt (102)	1923–35	315	12	3.8	151	9	6.0	Swe
Hesser (134, 135)	1929–35	210	12	5.7	94	3	3.2	Swe
Crohn & Lerner (133)‡	1927–37	147	14	9.5	29	0	0	U.S.
Graham et al. (74)	1929–38	134	20	15.4	59	3	4.7	Scot
Jankelson & Segal (137)	Prior to '38	165	19	11.5	35	2	5.9	U.S
Kirsner & Palmer (70)	1929–39	150	5	3.3	42	0	0	U.S
Franzen (121)	1928–40	333	15	4.5	217	9	4.4	Swe
Rafsky & Weingarten (82)	1927–41	345	29	8.7	63	7	11.1	U.S
Bohrer (79)†	Prior to '41	466	78	16.7	82	14	17.4	U.S
Thorstad (143)	1931–41	230	15	6.5	54	7	13.0	U.S
Jones, F. A. (109)	1940–42	122	10	8.2	39	4	10.3	Eng
Schiff (120)	Prior to '44	141	11	7.9	19	0	0	U.S
Baker (72)	1940–45	382	56	14.6	194	21	10.8	Eng
Total	..	3877	413	10.6	1376	114	8.3	

10.6 − 8.3 = 2.3; this is significant.

* Many articles do not permit such a comparison.

† Results of a questionnaire directed to surgeons.

‡ Used only the medical group, because data were incomplete on the surgical group.

mortality rate for gastric ulcer is 16.7 per cent and in the smaller s
7.9 per cent of patients who bleed. This shows, as previously indic
how widely the mortality varies significantly among hospitals, emphas
not so much a difference in treatment as a difference in the definitio
hemorrhage and in the nature of the population.

Table 72

SHOWING RELATION OF SEX AND SITE TO TENDENCY TO HEMORRHAGE IN PEPTIC ULCER

Author	*Period*	*Gastric Ulcer*						*Duodenal Ulcer*						*Country*
		Males			*Females*			*Males*			*Females*			
		No. Cases G.U.	*No. Cases Hem.*	*Per Cent Hem.*	*No. Cases G.U.*	*No. Cases Hem.*	*Per Cent Hem.*	*No. Cases D.U.*	*No. Cases Hem.*	*Per Cent Hem.*	*No. Cases D.U.*	*No. Cases Hem.*	*Per Cent Hem.*	
Manheim (91)	1915–25	138	34	24	42	19	45	223	39	17	23	9	39	U.S.A.
Ihre & Müller (85)	1930–40	157	52	33	100	28	28	655	132	20	233	42	18	Sweden
Alsted (71)	1935	16	3	19	6	0	0	83	21	25	26	8	..	Denmark
Total	..	311	89	28	148	47	32	961	192	20	282	59	21	..

There is no significant sex difference in the death rate from hemorrhage or bleeding tendency of a gastric or duodenal ulcer.

Relation of Sex to Hemorrhage in Peptic Ulcer

A significant sex difference in the tendency to bleed is not evident fro the available data (Table 70). However, a bleeding ulcer is slightly b significantly more hazardous in men than women on the average whe large number of cases are grouped together (Table 71). Twenty per ce of 7768 male and 20 per cent of 3893 female ulcer patients bled (Ta 70), and 10.6 per cent of 3877 males and 8.3 per cent of 1376 females w bled died (Table 71).

On the basis of the data available (Table 72), which are meager, th is no sex difference in the tendency to bleed from a gastric or duode ulcer (88). Neither do these particular sets of data show a significant difference in the mortality from bleeding gastric and duodenal ulcer.

Stolte (86) shows that in women as well as men the tendency to bl is greater the later the ulcer begins. The frequency of bleeding in suc sive decades shows no sex difference (Table 66).

Relation of Age to Incidence and Mortality from Hemorrhage

Except during the first year, the tendency to bleed does not cha during the first four decades (Table 66) during the disease. The la incidence during the first year is probably due to the hemorrhages wh occur without prior symptoms (16 per cent of cases). The increase sh in Table 66, Part A, during the fifth and sixth decades is not statistic significant. However, when the actual frequency of hemorrhage decade is calculated, it is found (Table 66, Part C) that the frequency increase with age, particularly after 40 years of age. This, Stolte shows, is due to the fact that an ulcer which starts late in life is more pr to bleed than one that starts early in life (Table 73).

However, the physician sees more patients with bleeding ulcers w age ranges from 40 to 60 years of age and these are the decades du which most deaths occur (Table 74). Nevertheless, the older the pat the more hazardous it is to have a hemorrhage (Table 74). The increa hazard forms almost a straight line from the age of 10 to 80 years.

Many authors do not supply both the mortality and number of of hemorrhage by decades which would permit a more accurate ave picture than that given by the data in Table 74. More authors give mortality below and above 40, 45, or 50 years of age but, as will be n in Table 75, some do not similarly divide their total cases of hemorrh Nevertheless, the data so arranged show that 80 per cent of deaths bleeding ulcer occur above the age of 40 and 70 per cent above the a 50. This comparison is obviously not as valuable as the following com

rom Table 76, namely; the relative average mortality of bleeding ulcer atients below 40 years is approximately 4 per cent and above 40 years per cent; or below 50 years 5 per cent, and above 50, 15 per cent.

Table 73

REQUENCY OF HEMORRHAGE IN SUCCEEDING DECADES IN RELATION TO THE AGE OF THE PATIENT AT THE ONSET OF DISEASE IN 320 PATIENTS*

	Age of Patient							
	0–20	*20–30*	*30–40*	*40–50*	*50–60*	*60–70*	*70–80*	*80+*
t of Disease before 30 yr.								
ears of Disease	215	716	626	286	130	35	1	..
eedings	9	20	30	16	9	9	..	..
rcentage	4.2	2.8	4.8	5.6	6.9	..	..	..
t of Disease before 50 yr.								
ears of Disease	..	..	404	573	202	44	3	..
eedings	..	..	30	46	22	5	..	..
rcentage	..	..	7.4	8.0	10.9	11.4	..	..
et of Disease after 50 yr.								
ears of Disease	..	..	..	..	179	154	67	4
leedings	..	..	..	..	16	22	17	1
ercentage	..	..	..	..	9	14.4	25.4	..

In this table the cases are presented according to age at the beginning of the disease.
* Stolte (81).

Men tend to bleed from their ulcer at a younger age than women, ough the difference is not significant, as Ihre and Müller (85) found. No nificant sex difference is evident in the rate of mortality increase with e, according to the data available (Table 76).

It is sometimes stated today that duodenal ulcer tends to bleed and use death at a younger age than gastric ulcer. There is no good evidence support this statement, because the data in the literature are too eager (89–91). As will be shown later, the reverse was true of women or to 1915. This impression probably arises from the fact that more eeding duodenal ulcers are seen. The questionnaire results of Bohrer 0) reveal that in 222 cases of bleeding duodenal ulcer, 16 or 7 per cent deaths occurred below 45 years of age and in 67 cases of bleeding gastric cer, 7 or 10 per cent of deaths occurred, a difference that is not significant.

THE CHANGED INCIDENCE OF HEMORRHAGE FROM PEPTIC ULCER

Since the latter part of the last century, a change has occurred in the incidence of manifest hemorrhages from peptic ulcer.

Table 74

SHOWING FREQUENCY OF MORTALITY FROM HEMORRHAGE FROM PEPTIC ULCER BY DECADES OF AGE

Age	*0–9*		*10–19*		*20–29*		*30–39*		*40–49*		*50–59*		*60–69*		*70–79*		*80+*	
Author	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*	*No. Cases Hem.*	*No. Deaths*
Burger & Hartfall (78)	..	..	5	1	19	1	27	3	37	13	36	9	11	3	2	1	..	..
Goldman (96)	..	..	2	0	39	1	72	3	115	12	82	10	54	11	24	1	..	..
Baker (72)	..	..	5	1	37	6	79	11	132	20	155	23	121	13	38	3	..	..
Hesser (134)	2	0	31	0	85	0	92	2	111	4	107	6	59	5	23	9	2	2
Jones, F. A. (109)	..	..	1	..	5	1	20	0	40	1	47	3	37	8	8	1	3	0
Hellier (90)	..	..	6	..	35	4	51	6	68	7	54	10	18	3	..	..	..	..
Allen & Benedict (105)	..	..	..	..	20	1	33	1	34	2	22	9	6	5	2	1	1	1
Total	2	0	50	2	240	14	374	26	537	59	513	70	306	48	97	16	6	3
Per Cent Mortality	0		4.0		5.8		7.0		11.0		13.6		15.7		16.5		50	

SHOWING THE RELATIVE MORTALITY OF A HEMORRHAGE FROM PEPTIC ULCER WHEN IT OCCURS BELOW OR ABOVE THE AGE OF [illegible]

50 YEARS

Author	40 Years						45 Years						50 Years						
	Below			Above			Below			Above			Below			Above			
	No. Cases Hem.	No. Deaths	Per Cent	No. Cases Hem.	No. Deaths	Per Cent	No. Cases Hem.	No. Deaths	Per Cent	No. Cases Hem.	No. Deaths	Per Cent	No. Cases Hem.	No. Deaths	Per Cent	No. Cases Hem.	No. Deaths	Per Cent	
Thorstad (143)	..	..	..	..	..	..	95	4	..	189	17	..	..	..	..	..	..	..	..
Bohrer (79)	..	..	..	..	..	..	290	27	..	371	75	..	..	..	..	..	..	..	..
Blackford & Cole (94)	..	..	..	..	..	..	124	3	..	84	6	..	..	..	..	..	..	..	..
Rafsky & Weingarten (82)	..	..	..	..	..	..	..	..	..	..	..	..	270	13	..	138	23	..	..
Baker (72)	121	7	..	455	70	..	..	..	..	..	..	..	213	18	..	323	59	..	..
Kirsner & Palmer (70)	105	3	..	125	4	..	..	..	..	..	..	..	167	3	..	64	4	..	..
Mossberg (110)	124	8	..	179	38	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Hesser (134)	210	2	..	302	27	..	..	..	..	..	..	..	321	6	..	191	23	..	..
Jones, F. A. (109)	22	1	..	100	14	..	..	..	..	..	..	..	54	2	..	68	13	..	..
Franzen (121)	174	2	..	420	22	..	..	..	..	..	..	..	288	3	..	266	21	..	..
Burger & Hartfall (78)	51	5	..	86	26	..	..	..	..	..	..	..	88	18	..	49	13	..	..
Hellier (90)	87	10	..	140	20	..	..	..	..	..	..	..	155	17	..	72	13	..	..
Allen & Benedict (105)	53	2	..	65	18	..	..	..	..	..	..	..	97	4	..	31	16	..	Duodenal
Holman (151)	30	4	..	60	8	..	..	..	..	..	..	..	60	7	..	30	5	..	ulcer only
Christiansen (100)	128	5	..	161	18	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Goldman (96)	113	4	..	275	34	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Total	1218	53	4.3	2368	299	12.6	509	34	6.7	644	98	15.1	1713	91	5.3	1232	190	15.4	..
Ihre & Müller (85)	..	0	..	..	10	..	..	..	..	..	..	..	..	4	..	.	14	..	..
Enocksson (77)	..	3	..	..	11	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Kalk (84, 124)	..	1	..	..	15	..	..	..	..	..	..	..	..	3	..	..	21	..	..
Meulengracht (106)	..	1	..	..	25	..	..	..	..	..	..	..	..	7	..	..	19	..	..
Hansen & Pedersen (152)	..	51	..	..	342	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Grand Total	..	109	(12.2) of hem. deaths below 40 yrs.	..	702	..	..	34	(25.7) of hem. deaths below 45 yrs.	..	98	..	..	105	(30.1) of hem. deaths below 50 yrs.	..	244	..	..

Table 76

Showing Frequency and Mortality from Hemorrhage from Peptic Ulcer by Decades of Age and Sex

Age	0–9		10–19		20–29		30–39		40–49		50–59		60–69		70–79		80+	
Author	No Cases Hem	No Deaths	No Cases Hem	No Deaths	No Cases Hem	No Deaths	No Cases Hem	No Deaths	No Cases Hem	No Deaths	No Cases Hem	No Deaths	No Cases Hem	No Deaths	No Cases Hem	No Deaths	No Cases Hem	No Deaths
Males																		
Berger & Hirschfeld (38)			1		8	1	19	2	28	11	28	5	9	3	2	1		
Baker (22)			4	0	28	1	56	5	96	9	93	17	82	17	21	5	2	2
Jones, F. A. (1907)			1	0	4	1	17	0	32	1	34	2	27	1	3	1	2	0
Hellier (96)			4	0	25	4	38	6	28	3	29	6	12	2		6		0
Totals			10	0	65	7	130	13	194	24	184	34	130	23	28	1	4	2
Per Cent Mortality	0		0		11.5		10.0		12.1		18.4		20.7		25.0		50.0	
Females																		
Berger & Hirschfeld (38)			4	1	11	0	8	1	9	2	8		2		1			
Baker (22)			1	0	9	0	24	1	32	2	42	5	43	6	17	2	1	1
Jones, F. A. (1907)					1	0	1	0	2	0	13	1	15	2	4	0	1	0
Hellier (96)			2	0	6	0	7	0	23	4	17	4	3	1	5	0	2	0
Totals			7	1	27	0	42	2	74	8	82	10	63	9	27	2	4	1

Table 77

ATIVE CLINICAL FREQUENCY OF HEMORRHAGE FROM PEPTIC ULCER IN MEN AND WOMEN*

Author	Period	No. Cases: Hem. Both Sexes	Men		Women		Geographic Location
			No. Cases Hem.	Per Cent	No. Cases Hem.	Per Cent	
	1943–47	62	15	24	47	76	Copenhagen
Joslin (87)	1888–98	187	30	16	157	84	Boston
	1896–1902	496	59	15	347	85	Copenhagen
	1897–99	246	44	18	202	82	London
	1897–1902	500	98	20	402	80	London
	1910–17	890	322	36	568	64	Lund, Malmo, Sweden
	1896–1914	71	24	34	47	66	Copenhagen
	1902–26	467	160	34	307	66	Birmingham, England
Period		2823	752	27	2071	73	
	1899–1936	704	309	57	302	43	Holland
	1915–25	101	73	73	28	28	New York
severe cases) (77)	1913–21	115	68	59	37	41	Sweden
	1916–32	624	282	59	172	41	Oslo, Norway
and Period		1341	792	59	539	41	
rshall (78)	1921–30	137	95	70	42	30	Guy's, London
29)	1925–31	191	137	72	54	28	London
	1926–31	111	80	72	31	28	Birmingham, England
(100)	1923–32	289	211	73	78	27	Copenhagen
	1926–32	171	120	..	50	..	Leeds, England
135)	1925–35	304	210	69	94	31	Sweden
9)	1923–35	466	315	..	151	..	Sweden
	1925–35	1159	788	68	371	32	Copenhagen
	1931–35	206	144	70	62	30	Copenhagen
L (74)	1929–38	193	131	68	62	32	Glasgow
1)	1928–40	550	333	62	217	38	Lund, Sweden
er (85)	1930–40	254	184	73	70	27	Stockholm
ean Period, m)	..	4031	2748	65.6	283	34.4	..
mer (111)‡	1927–37	176	147	84	29	16	New York
Segal (137)	Prior to '38	200	165	82	35	18	Boston
mer (70)	1929–39	192	150	78	42	22	Chicago
	1936–39	236	184	78	52	22	Holland
cHardy (127)	Prior to '39	131	105	80	26	20	New Orleans
ingarten (82)	1927–41	408	345	84	63	16	New York
3)	1931–41	284	230	81	54	19	Detroit
	Prior to '41	548	466	85	82	15	U.S.A.
109)	1940–42	161	122	76	39	24	London
	1940–45	120	80	66	40	34	London
Tracey (145)	Prior to '46	140	125	89	15	11	Lahey Clinic
	1937–43	160	141	88	19	12	Cincinnati
(98)	1937–48	230	192	83	38	17	Chicago
rd Period, U.S.A.)	..	2986	2452	83	534	17	..

not a true sex frequency, since it does not consider the sex distribution of the patients admitted

Ihre and Müller (85).

by medical group.

This change in sex incidence of manifest hemorrhage has been poi out by a number of authors. It is quite evident from the data arrange Table 77. Prior to World War I, approximately 70 per cent of the cas manifest hemorrhage in Denmark, Sweden, the United States, Engl and Germany occurred in women and in young women (92). For exan Greenough and Joslin in Boston reported 157 cases of gastric ulce women and 30 in men, the peak incidence of hematemesis occurring 20 to 30 years of age in the women. Since World War I, more men women have manifest hemorrhages.

Table 78

AGE AT ONSET OF THE FIRST HEMORRHAGE IN PEPTIC ULCER PATIENTS CLASSIFI ACCORDING TO SEX*

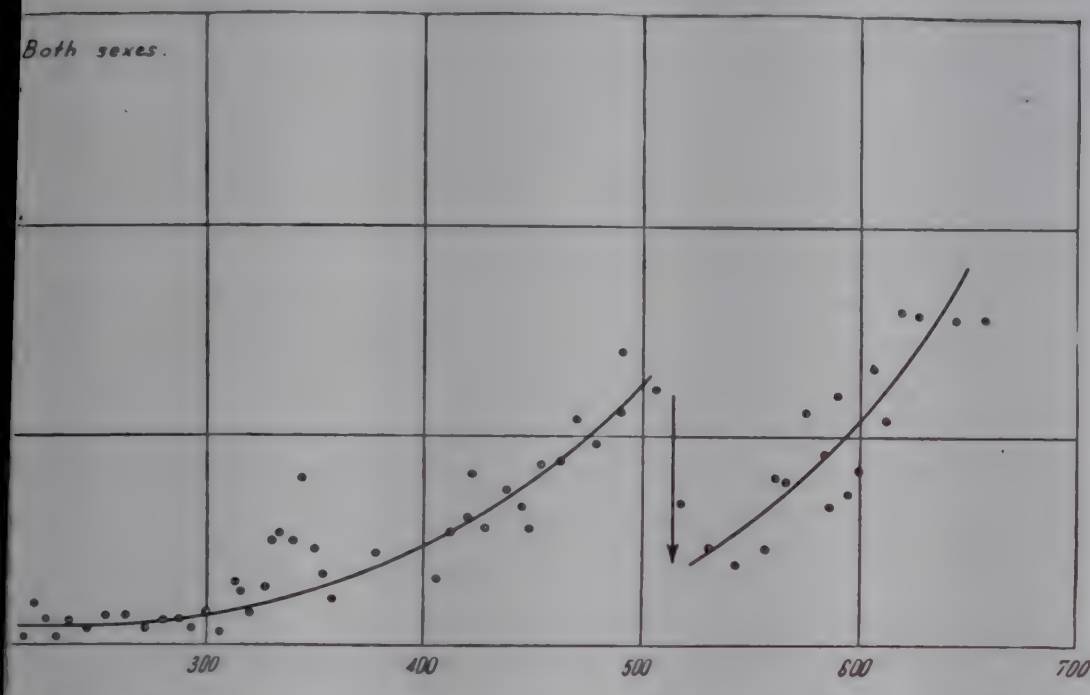
Age of Bleeders among Ulcer Patients at First Hemorrhage due to Peptic Ulcer According to Period of Hospitalization

Period	No. Males	No. Females	1st Hemorrhage Before						
			Age 30 Per Cent		Age 40 Per Cent		Age 50 Per Cent		Age Per C
			M	F	M	F	M	F	M
Before 1915	57	120	15.8	45.8	42.1	70.0	68.4	83.3	91.2
1915–1919	69	48	23.2	20.8	52.2	39.6	75.4	64.4	89.9
1920–1935	194	100	21.1	28.0	49.5	49.0	67.5	74.0	87.1
1936–1939	119	51	15.1	5.9	40.2	25.5	63.9	41.2	79.8

* Stolte (86).

Stolte (86) has presented striking data from Amsterdam whi shown in Table 78. Prior to 1915, twice as many females as males admitted; since 1920, the reverse has been the case. The inciden hemorrhage in male patients has remained constant as regards the d in which the first hemorrhage occurs. Prior to 1915, females had thei hemorrhage prior to an age of 30; more recently, it occurs about th of 30. This occurred regardless of improved diagnostic methods a increased admission of all types of patients to hospitals.

Alsted (71) has made a special study of cases of manifest hemor in Copenhagen and finds an increase in the total incidence of m hemorrhage since 1900, except for a short period during World W after which the rise continued at its previous rate. This increase wa siderably greater than the rate of growth of the population. It app both men and women, chiefly men, and was accompanied by a



G. 99. Cases of hematemesis in relation to the population of Copenhagen. abscissa indicates the population in thousands; the ordinate the number of There is one dot for each year and the arrow indicates the fall that occurred 17.

ase in the incidence of melena and a less marked increase in he-mesis. A portion of the increase in hemorrhage was accounted for by ncrease in the incidence of ulcer and by an increase in the frequency eeding.

Table 79

SHOWING RELATION OF HEMORRHAGES FROM PEPTIC ULCER TO MONTHS AND SEASONS

Author	*Jan.*	*Feb.*	*Mar.*	*Apr.*	*May*	*June*	*July*	*Aug.*	*Sept.*	*Oct.*	*Nov.*	*Dec.*	*Country*
en (121)	45	37	33	34	44	39	57	39	54	55	60	53	Denmark
(72)	7	8	6	5	3	6	5	6	8	7	8	8	England
n (154)	5	11	4	5	6	2	2	4	4	3	2	4	U.S.A.
son (112)	51	34	42	36	51	39	49	42	64	92	58	73	Sweden
ger et al. (155)	33	32	23	25	15	28	22	25	33	29	37	34	Norway
d (129)	38	26	41	27	32	33	36	36	34	43	31	47	..
als* (by month)	179	148	149	132	151	147	171	152	197	229	196	219	..
als (by trimesters)	608				621				841				..
erg (110)	81				104				133				Sweden
iansen (100)	101				87				101				Denmark
nd Total (by trimesters)	790				812				1075				..

Mean 172.5 ± 19.93.

The most remarkable observation made by Alsted was the decrea the frequency of hemorrhages during World War I (1916–17) in Co hagen (Fig. 99). This, like the change in the sex incidence of the dis can only be accounted for by an environmental change.

Relation of Hemorrhage to Months and Seasons

The data available on the relation of hemorrhage to the months seasons are collected in Table 79. When all the cases are added togeth significantly greater incidence is evident in the fall months; very st tically significant peaks occur in October, November, and December. fact that so many cases are required to demonstrate a significant sea or periodic occurrence shows that the factor is not a very potent one.

It has been suggested by some who have observed an increased nu of cases in fall and winter that the increase was due to low vitam intake. That this is not the case is shown by the relatively low inci in February and March.

Miscellaneous Factors Claimed to Favor or to Predispose t Hemorrhage from Peptic Ulcer

War and Bleeding Ulcer. Melton (93) in 1940 reported Lewisham Hospital, London, 36 hemorrhages and 15 perforatio peptic ulcer during the first eight months of 1939; whereas 38 hemorr and 14 perforations occurred in the next four months, or the first months of the War.

Activity. Activity has been assumed to predispose to hemor from peptic ulcer. But Blackford and Cole (94) have reported tha thirds of 57 cases of massive hemorrhage occurred during a rela quiescent period. Factors such as the excessive use of alcohol, caffein tobacco and dietary indiscretions have been accused. Presumptive b convincing evidence has been provided to support such claims.

Hypertension. It has been suggested that hypertension predi to bleeding or excessive bleeding in peptic ulcer. For example, it ha explained that a high blood pressure would increase the amount bleeding from a small opening in an artery, or would cause a c softened area in an artery to blow out (72, 95).

The data which bear on this question are meager. Goldma found that 70 per cent of 38 deaths due to bleeding ulcer had a sclerosis; but arteriosclerosis may favor bleeding by loss of retractab the blood vessels rather than by hypertension; of course, both would presumptively favor hemorrhage. In fact, in the dog we kno retraction of a large artery plus a low blood pressure in consequ hemorrhage caused blood to cease flowing from the severed vessel.

The presence of a high blood pressure in a patient (over 150 systolic 90 diastolic) during a bleeding episode would indicate that the patient not lost much blood. Or, it might indicate a "reactive hypertension" mpensatory vasoconstriction) in a person otherwise having a normal d pressure. A normal blood pressure might indicate considerable loss ood in a person otherwise having hypertension, or a relatively small (500–750 cc.) in a normal person whose cardiovascular system has pensated for the decreased blood volume by vasoconstriction and ycardia (97). For example, Sullens, Steigmann, and Meyer (98) rved no deaths in patients with a blood pressure above 150 mm. Hg, ne contrary, 15 deaths (8.4 per cent) occurred in 178 patients with a d pressure of 100–150 systolic and 16 deaths (37 per cent) in 43 nts with a blood pressure of 90 systolic or below at the time of italization.

Table 80

COMPARATIVE MORTALITY BELOW AND ABOVE 50 YEARS OF AGE FROM BLEEDING PEPTIC ULCER WITH AND WITHOUT HYPERTENSION *

Age	*Hypertension during Bleeding Episode*				*Without Hypertension*				*Total*			
	No. Cases	*Per Cent in Age Group*	*No. Died*	*Mort. Per Cent*	*No. Cases*	*Per Cent in Age Group*	*No. Died*	*Mort. Per Cent*	*No. Cases*	*Per Cent in Age Group*	*No. Died*	*Mort. Per Cent*
r 50	31 ..	33 ..	3 1	10 12	319 ..	72 ..	10 9†	3.1 6.0	350 ..	64 ..	13 0	3.7 ..
50	61 ..	64 ..	9 3†	15 ..	133 ..	28 ..	20 6†	15 ..	194 ..	36 ..	29 1†	15.0 ..
tal	92 ..	.. ..	12 4†	.. ..	452 ..	.. ..	30 15†	.. ..	544 ..	.. ..	42 1†	.. ..

From Rafsky & Weingarten (82).
Excluded death with complicating diseases.

The best data, because the factor of age is considered, have been vided by Rafsky and Weingarten (99); they are presented in Table 80. vill be noted that when the patient is over 50 years of age, the presence absence of hypertension has no effect on mortality, the mortality being per cent in both instances. Below 50 years, the mortality of the hyper-sive group was 10 per cent (gross 12 per cent) and of the non-hyper-sive group 3.1 per cent (gross 6.0 per cent). This difference, probably

due to the few cases, is not quite significant statistically. So, hyperte in patients under 50 years of age may tend to increase mortality, t definite conclusion is not warranted at present.

Gastric Acidity. Several authors have reported results on the a of the gastric contents as determined by the Ewald or fractional test-: From 20 to 60 per cent of cases fall in the hypernormal range of ac Achlorhydria is occasionally found, which does not mean that it present prior to the hemorrhage. As indicated in the discussion of pe tion (p. 555), the amount of acid secreted is also important. It is clea an ulcer may bleed when the acidity of the gastric contents afte hemorrhage is within the normal range (74, 78, 100–102).

Hemorrhage and Pain in Ulcer

It is frequently stated that a hemorrhage relieves ulcer pain whe present prior to a large hemorrhage. In 55 cases reported by Burge Hartfall (78), only 15 had relief from pain, no record being made o in 67 other cases. In 202 cases reported by Rischel (4), 175 h. dyspepsia after suffering hemorrhage and being placed promptly puree diet. This result is to be expected since diet and bed rest u relieve the distress of peptic ulcer. When hemorrhage does dramat relieve the pain, the relief may be due to the buffering of acid b blood, the enforced rest in bed, and the general relaxation second the weakness following hemorrhage, just as after a good night's re ulcer patient awakens in the morning without pain.

Length of Period between Onset of Fatal Hemorrha and Death

The length of this period varies considerably and the data provi the literature are too heterogeneously presented to tabulate. Tixi Clavel (103) have reported that 40 per cent of the cases die within days. Finsterer (104) states that the third day is critical. Alle Benedict (105) and Christiansen (100), observing 23 and 20 respectively, found that the average premortem duration after the of the fatal episode was 16 days. Meulengracht (106) lost 16 of his 2 between the second and tenth day and 21 cases within the first 1 One gains the impression from the data as presented that the firs 72 hours are critical and that half of the fatal cases die within a wee the onset of the fatal hemorrhage.

Gross Morphology of a Bleeding Peptic Ulcer

Bleeding peptic ulcers are chronic in type in approximately 66 p and acute in 28 per cent of the cases (Table 81).

Table 81

INCIDENCE OF ACUTE AND CHRONIC ULCERS IN FATAL HEMORRHAGE

Author	*No. Acute Ulcers*	*No. Chronic Ulcers*	*Acute + Scars*	*Undetermined*
(156)	16	21	11	7
(90)	4	18	9	..
& Hartfall (78)	15	30	..	..
an (128)	13	17	..	..
157)	61	163	..	..
A. (109)	8	5	..	..
2)	9	43	..	..
	126	297	20	7
ent	28.0	66.1	4.4	1.5

netimes at autopsy or, particularly, at surgery a bleeding point t be found. When a definite bleeding point is not discovered, is or duodenitis with erosions are usually present. In rare instances, is is said not to be present. A number of articles are to be found literature on the subject of large hemorrhage of obscure origin In one instance, we have seen a dog with a pyloric pouch and a ng tendency of unknown cause and on two occasions blood flowed the mucosa of the pouch in a manner simulating the flow of sweat the skin. A histologic section showed red blood cells leaving the aries and passing between the cells lining the pyloric glands to the of the gland.

fatal hemorrhages, the pancreatoduodenal or the left gastric or epiploic artery lies opened in the base of the ulcer. The fact that the is generally opened only on one side prevents it from retracting. connective tissue and loss of elasticity would also prevent retraction

is well for therapeutic and prognostic reasons to remember that ulcers frequently are the cause of fatal hemorrhage and that arteries ly partially opened, not completely severed.

HEMORRHAGE FROM ANASTOMOTIC ULCER

eeding following gastroenterostomy and gastric resection usually tes an anastomotic ulcer. A recurrent or persistent gastric or duo- ulcer or erosive gastritis are occasionally responsible, and sometimes use can be found. Jones (109) at autopsy on nine patients with

gastrojejunostomy who had died from hemorrhages found that in si hemorrhage came from a duodenal ulcer. However, most authors that anastomotic ulcer is the principal cause of hemorrhage foll gastric surgery. Thus, Cooper found that of 28 cases of postope hemorrhage, one represented a bleeding duodenal ulcer, one a ble gastric ulcer, and the remainder anastomotic ulcers.

Table 82

RELATION OF POSTOPERATIVE HEMORRHAGE TO PREOPERATIVE HEMORRHA

Authors	*Patients Who Bled Preoperatively*			*Patients Who Did Bleed Preoperative*		
	Number of Cases	*Number Who Bled Post-operatively*	*Per Cent Who Bled Post-operatively*	*Number of Cases*	*Number Who Bled Post-operatively*	*P W op*
Cooper	76	12	15.8	214	16	
Church and Hinton	15	7	46.6	91	15	
Eliason and Johnson	37	4	10.8	114	2	

* From Ivy and Fainer (159).

Late postoperative hemorrhage occurs more frequently after op on ulcer patients who bled preoperatively. Table 82 indicates that t constant trend. Three different authors, although presenting different incidences of hemorrhage, all have had a significantly incidence of hemorrhage in patients who bled preoperatively. Th add evidence to the suggestion that some ulcer patients are very p bleed.

We (159) have collected a number of studies on anastomotic which are shown in Table 83. It shows that 555 of 1593 patients, per cent of patients with anastomotic ulcer, had manifest hemorr some time in the course of their disease. The individual percentage between 13 and 59 per cent. While some of these series include on verified at surgery, the clinics which report them operate on al patients with an anastomotic ulcer.

Hemorrhage from an anastomotic ulcer tends to manifest melena, although hematemesis may occur, either with melena o

Bleeding from an anastomotic ulcer appears to have a n slightly less than that accompanying gastric or duodenal ulcer (T and 56). In Table 83, it is seen that 5.5 per cent of 256 patie anastomotic ulcers died from hemorrhage. However, this p

sents all cases of manifest hemorrhage, rather than a select or severe), and the lower mortality rate may be only apparent.

Table 83

BLEEDING ANASTOMOTIC ULCER*

Author and Year	Source of Material	Anastomotic Ulcer				
		Number of Cases	Number Bleeding	Per Cent Bleeding	Number Deaths	Per Cent Deaths
., 1928	Proved & Suspected	42	61	38	..	..
t & Stewart, 1929	Proved & Suspected	..	42	..	1	2.4
oni, 1932	Proved, Surgical	52	31	59	..	..
dict, 1933	Proved & Suspected	36	21	59	..	..
& Hoerner, 1935	Proved, Surgical	597	201	34	..	..
y & Swinton, 1935	Proved & Suspected	30	4	13	..	..
ht, 1935	Proved & Suspected	458	124	30	7	5.6
se, 1937	Proved & Suspected	30	7	23	..	..
ı, 1937	..	..	35	..	2	5.7
st & Ryle, 1937	Proved & Suspected	157	72	46	..	..
lotto, 1940	X-ray Diagnosis	31	6	19	..	..
son, 1945	Proved & Suspected	21	10	48	..	..
nhoff, 1945	Proved & Suspected	23	8	33	..	..
ısgaard, 1946	Proved & Suspected	70	29	41	1	3.4
per, 1948	Proved & Suspected	46	26	57	3	11.5
otals	..	1,593	555	34.8	14	5.5

* Revised from Ivy and Fainer (159).

SUMMARY

Hemorrhage is the most frequent complication of peptic ulcer and the ond leading cause of death. However, the literature varies considerably arding the incidence of and mortality from hemorrhage, partly because the difficulty in defining terms as to the extent of hemorrhages. Until problem of diagnosis of the extent of hemorrhage is solved to the isfaction of all, it would appear best to compare mortality and incidence the basis of "manifest hemorrhage."

Approximately 72 per cent of manifest hemorrhages from the upper mentary tract are due to peptic ulcer. About 25 per cent of patients mitted to hospitals for peptic ulcer are admitted for hemorrhages. This rrelates with the clinical incidence, which shows that about 25 per cent peptic ulcers bleed sometime in their course. About 7.5 per cent of

bleeding ulcers prove fatal, and 1.6 per cent of patients with pep die from hemorrhages. Some authors more recently report a mo low as 1.5 per cent of all patients with manifest hemorrhage. It is to determine the relation of mortality to the hemoglobin or the cry estimation; it is possibly unreliable in acute bleeding. Continued rent hemorrhage, particularly after entering the hospital, portend outcome. Approximately 33 per cent of the patients admitted to for bleeding are suffering a recurrence of bleeding. Bleeding ulcer relapse by bleeding more frequently than nonbleeding ulcer pat

An average of 16 per cent of patients experience hemorrhag first sign of an ulcer, but most ulcers cause distress for a long perio a hemorrhage occurs. The longer the duration of ulcer disease, th is the chance for a hemorrhage to occur. However, some pat apparently more prone to bleed than others. Since 1912 more ulcers were duodenal than gastric in the United States, the ra 4 D.U.:1 G.U. The incidence was reversed before that time. In as late as 1935, more bleeding ulcers were gastric ulcers than duo England, more bleeding ulcers are gastric in some areas and m denal in others. Environmental factors are undoubtedly involved. ulcers bleed more commonly than duodenal, but the difference dence is slight; the difference in mortality shows a bleeding gas to be about twice as hazardous as a bleeding duodenal ulcer.

No significant sex difference in the incidence of bleeding apparent in recent years, but bleeding in the male ulcer patient is more hazardous.

An ulcer which starts late in life is more prone to bleed than o starts early in life. For this reason, a bleeding ulcer in an older in is more hazardous. The relative average mortality of bleeding patients below 40 years is approximately 4 per cent and above 40 cent; or below 50 years, 5 per cent and above 50, 15 per cent.

A change in incidence of hemorrhage from peptic ulcer has o Prior to World War I, 70 per cent of manifest hemorrhages occ young women, with the first hemorrhage occurring frequently b age of 30. Since World War I, more men than women have had hemorrhage and the first hemorrhage in women now occurs usual the age of 30. This change in sex incidence can only be accounte an environmental change.

The incidence of hemorrhage is greater during the fall months in the northern hemisphere. Since this is not a consistent finding, mental factors probably vary in different populations. The hei war strain in Europe increased the incidence of hemorrhage fro ulcer as it did of perforation. The presence of hypertension

ntly increase either the incidence or fatality of hemorrhage from
lcer, according to the evidence available, when the patient is above
of age. When below 50 years of age, hypertension may increase
ality. The presence of acid appears to be essential for the occur-
hemorrhage but there is no evidence showing that an excessive
is essential.

atal hemorrhage, as a rule, the pancreatoduodenal, or the left
or the gastroepiploic artery lies opened in the base of the ulcer and
retract because of being opened on only one side, or because it is
dense connective tissue, or because it has lost elasticity due to
clerosis or endarteritis.

incidence of bleeding from anastomotic ulcer is difficult to deter-
view of the frequent uncertainty regarding whether the original
al or gastric ulcer, a new duodenal or gastric ulcer, or an anas-
ulcer is bleeding. Approximately 32 per cent of patients with the
is of an anastomotic ulcer bleed. Bleeding from an anastomotic
not so hazardous as bleeding from a gastric or duodenal ulcer.

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OUTLINE OF CHAPTER 17

Clinical and Constitutional Aspects of Pathogenesis

I. Clinical Incidence of Peptic Ulcer
   A. incidence in limited populations
   B. changes in clinical incidence
   C. changes in clinical incidence relative to sex of and site of ulcer
   D. present discrepancy between clinical impressi mortality statistics relative to the frequ gastric and duodenal ulcer
   E. new type of ulcer
   F. age of onset of symptoms from duodenal and ulcer
   G. peptic ulcer mortality according to sex and a
   H. relation of population density to deaths from ulcer
   I. social class and mortality from peptic ulc cancer
   J. effect of marital state on mortality from ulcer
   K. relation of incidence of peptic ulcer to mo year
   L. effect of heavy air raids and war on incidence mortality from peptic ulcer
   M. environmental factors suspected of causing o peptic ulcer and its recurrences

II. Relation of Other Diseases to Peptic Ulcer
   A. appendicitis and cholecystitis
   B. oral sepsis
   C. upper respiratory infections and tonsillitis
   D. relation of activity of an ulcer to presi bacteria in its margins and base
   E. cirrhosis of the liver
   F. diabetes mellitus

ARDIOVASCULAR DISEASE
1. Organic Disease
2. Functional Disease
a. Angiospastic or Vasomotor Diathesis
SSOCIATION OF POLYCYTHEMIA AND PEPTIC ULCER
PASTIC OR DYSKINETIC COLON
HLOROSIS
STITUTIONAL FACTOR IN PEPTIC ULCER
NTRODUCTION
IEREDITARY TRANSMISSION OF ULCER
RACIAL SUSCEPTIBILITY TO ULCER
CAUSAL MECHANISMS OF HIGH SUSCEPTIBILITY TO PEPTIC ULCER
1. Anatomic Suggestions
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BODY BUILD OR HABITUS AND PEPTIC ULCER
HYPERSTHENIC AND HYPOSTHENIC GASTRIC DIATHESIS
DIFFERENCE IN SEX INCIDENCE
PEPTIC ULCER IN INFANTS AND CHILDREN IN RELATION TO THE QUESTION OF A CONSTITUTIONAL FACTOR
1. Types of Ulcer in Infants and Children
2. Frequency of Peptic Ulcer in Infants and Children
a. Clinically
b. At Autopsy
3. Site of the Ulcer
4. Complications
5. Anastomotic Ulcer
THEORIES OF CAUSE OF ULCER IN INFANTS
ON THE SEX RATIO OF PEPTIC ULCER IN INFANTS AND CHILDREN AND ITS SIGNIFICANCE
CONCLUSION
THE IDENTITY OF GASTRIC AND DUODENAL ULCERS
EXPERIMENTAL EVIDENCE
ANATOMIC EVIDENCE
EVIDENCE FROM PATHOLOGIC PHYSIOLOGY
CLINICAL EVIDENCE
MARY

CHAPTER 17

Clinical and Constitutional Aspects of Pathogenesis

Clinical Incidence of Peptic Ulcer

Observations made on the clinical incidence of peptic ulcer are by necessity confined to limited populations. This is true also of autopsy studies but clinical studies are usually more narrowly limited than post-mortem studies.

Incidence in Limited Populations

Jennison (1) made a study of the employees of the Metropolitan Life Insurance Company for a period of 10 years. There were 13,885 employees, 3965 males and 9920 females, above the age of 17 years, 70 per cent being under 30 years. This study has the defect of dealing with data chiefly from clerical workers. One hundred ninety-one had duodenal ulcer and 14 had gastric ulcer (13.5 DU:1 GU). The total incidence of peptic ulcer in the group was 1.48 per cent. One hundred twenty-two males and 69 females had duodenal and 11 males and three females had gastric ulcer. The incidence in males, then, was 3.4 per cent and in females 0.7 per cent. A total of 101 ulcers (males: 67 DU and 11 GU; females: 20 DU and 3 GU) occurred in 2125 males and 2155 females *above 30 years of age;* or 3.67 per cent in males and 1.07 per cent in females. Above 20 years of age, there were 12,700 employees, 3900 males and 8800 females, with 183 ulcers (125 males and 58 females), yielding a total incidence of 1.44 per cent, and an incidence for males and females of 3.2 and 0.6 per cent respectively.

The incidence of complications in Jennison's group of 205 ulcers was 10.5 per cent from hemorrhage (20 cases), 2.6 per cent from obstruction (five cases), and 1.6 per cent from perforation (three cases). Most patients had their first symptoms between 20 and 40 years of age, and approximately one half treated themselves for two years before consulting a physician.

Alsted (2) has reported the incidence of ulcer in October 1940 in Denmark, when the Public Health Administration asked each physician to submit a list *for that month* of patients with peptic ulcer. This may not have revealed all patients, since some treat themselves and others have silent

ulcers. These data showed an incidence of 12 to 13 in 10,000 or 0.12 to 0.13 per cent for all inhabitants of Copenhagen and towns and urban areas and 0.087 per cent for rural areas. In males in cities, the incidence was 0.2 per cent; in rural areas, 0.12 per cent. In women in cities, the incidence was 0.06 per cent; in rural areas, 0.048 per cent.

Knutsen and Selvaag (3) had an opportunity to study the incidence of peptic ulcer in Drammen, Norway, a town of 25,830 persons, in 1942. Everyone with peptic ulcer had to turn in a card for special rations and the ulcer had to be radiologically demonstrable. Of the inhabitants, 21,918 were above 15 years of age. Five hundred thirty-seven ulcer patients were present, or a total incidence of 2.08 per cent. Above 15 years of age, the incidence was 2.45 per cent; above 20 years, 2.66 per cent; above 30 years, 2.74 per cent. If 19 cases of hematemesis and melena were to be added as due to peptic ulcer, the incidence in persons above 15 years of age would be 2.54 per cent. Operations had been performed upon 7.2 per cent of the patients with gastric ulcer and 5 per cent of those with duodenal ulcer. The sex ratio for peptic ulcer was 2.98 M:1 F. The sex ratios for gastric and duodenal ulcer are given in Table 84. Regarding age, gastric ulcer

Table 84

SEX INCIDENCE OF GASTRIC AND DUODENAL ULCER IN PERSONS ABOVE 20 YEARS OF AGE LIVING IN DRAMMEN, NORWAY, IN 1942*

	Total Incidence %	*Sex Incidence*		
		M %	*F* %	*Ratio*
Gastric ulcer	0.097	1.34	0.66	2.03:1
Duodenal ulcer	1.79	2.68	0.79	3.77:1
Ratio GU:DU	1:1.85	..	..	..

* Knutsen and Selvaag (3).

Juxtapyloric ulcers were counted as duodenal ulcers, because they believed they belong to the same class.

was represented principally in the age groups above 50 years and duodenal in lower age groups, the difference being greater in men. In the cities of Drammen and Stavanger, Norway, 0.33 per cent and 0.15 per cent of the population, respectively, were hospitalized annually in 1934 to 1936 for peptic ulcer (5).

We have, then, from these studies evidence for an incidence of peptic ulcer of approximately 2 to 3 per cent of the population above 15 or 20 years. Hansen (4) calculated that in Copenhagen the morbidity was 20

to 30 per 1000 of the entire population through the 30 year perio vestigated (1907–1936).

The survey on the incidence of chronic diseases made in 1937 by United States Public Health Service indicated that during that 320,000 persons had peptic ulcer. Since in that year the population a 20 years of age numbered 84.5 million, the incidence of peptic ulcer a time of the survey was 0.38 per cent. The same year the mortality rate 6.8 per 100,000 deaths (8786 cases), or 2.7 per cent of the ulcer cases c

Eusterman and Balfour (6) record that peptic ulcer was foun 14 per cent of 15,985 roentgenologic examinations at the Mayo Cli 2047 were duodenal and 167 were gastric. The ratio of duodenal ulc gastric ulcer to gastric cancer was 12: 1: 3. This represents a selected gr For example, 3.3 per cent of the admissions at the Mayo Clinic in were for peptic ulcer (7), whereas in the County Hospital, Chicago, figure is 0.88 per cent (1929–1936).

The autopsy incidence of peptic ulcer has been fully discusse Chapter 14.

We interpret the heterogenous evidence as indicating that from 10 per cent of most populations develop an ulcer in a lifetime, that total incidence of those afflicted at any one annual survey will vary f 1 to 3 per cent of the population above 20 years of age, and that from to 0.38 per cent of the population above 20 years of age will req hospitalization for treatment of ulcer annually.

Changes in Clinical Incidence

In Denmark, Hansen (8) studied the records of the outpatient, gical, and medical departments in Copenhagen between 1901 and 1 (Table 85). He found an increase in the incidence of peptic ulcer throu out. The increase was several times greater than could be accounted by an increase in population. It was not due to improvements in diagn or increased attendance at hospitals because the diagnosis of other ga disease, excluding gastric cancer, did not increase as much and becau reversal in sex incidence occurred. During the same period, the death in Denmark from peptic ulcer increased.

Alsted (9), in analyzing the data from a medical department i hospital in Copenhagen, came to the conclusion that the supposed incr in frequency since 1915 resulted from "improved diagnostic technique a growing number of readmissions." He believes that the number of f cases in men has remained about the same since 1919. In women a mar decrease in gastric ulcer has occurred. This can only be accounted fo some change in the environment of young women.

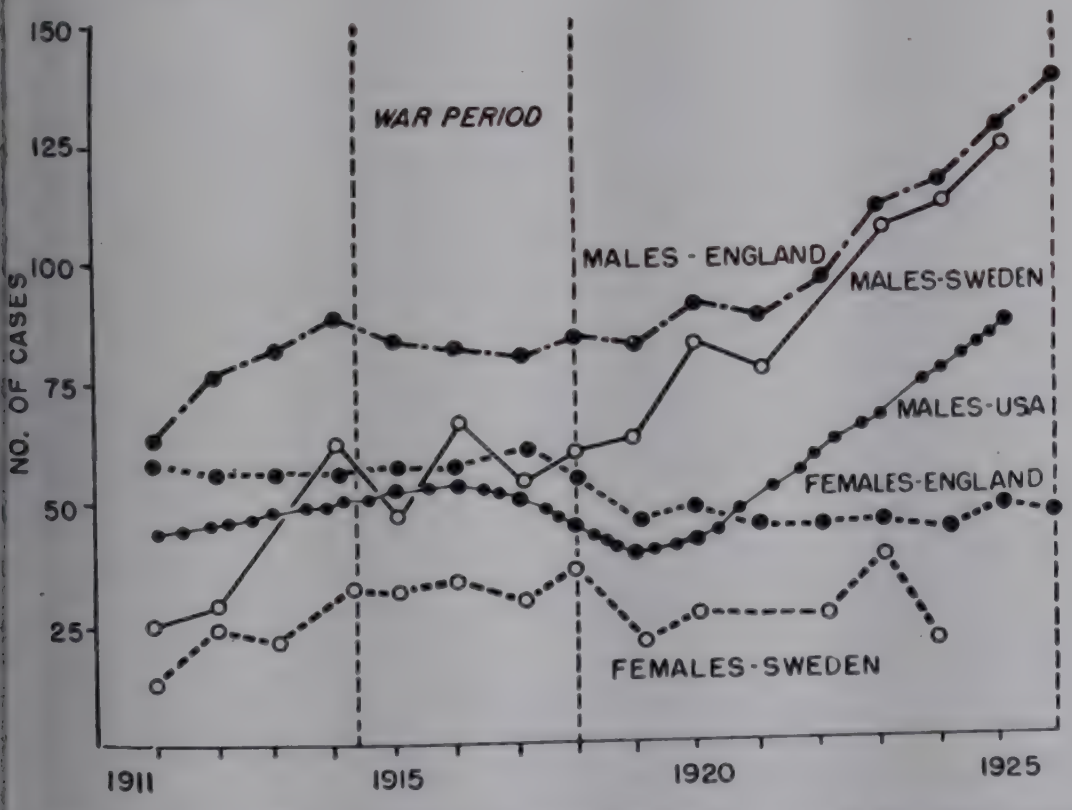
Most authors, when dealing with clinical ulcer statistics, fail to dif

Table 85

CLINICAL AND MORTALITY INCIDENCE OF PEPTIC ULCER BY SEX IN DENMARK*

Period	*Clinical Incidence in Copenhagen*			*Mortality in Denmark from Peptic Ulcer*		
	Men	*Women*	*Total*	*Men*	*Women*	*Total*
1901–05	100 (21%)	371 (79%)	471	..	..	..
1906–10	211 (32%)	441 (68%)	652	..	..	..
1911–15	458 (48%)	506 (52%)	964	130 (46%)	152 (54%)	282
1916–20	622 (50%)	627 (50%)	1249	195 (52%)	178 (48%)	373
1921–25	965 (65%)	528 (35%)	1493	388 (60%)	239 (40%)	627
1926–30	1303 (73%)	490 (27%)	1793	525 (68%)	241 (32%)	766
1931–35	1939 (76%)	620 (24%)	2559	879 (74%)	34 (26%)	1193

* Hansen (8).



. 100. Incidence of admissions to hospital for perforation in Sweden compared with mortality rates in England and U.S.A. during the period 1910–1925.

Table 86

MORTALITY AS RELATED TO SEX IN THE U.S.A. SINCE 1900*

Year	Total		Total No.		Rate		White		Negro
	No.	Rate	M	F	M	F	M	F	M
1900	534	2.7	269	265	2.7	2.7			
10	1912	4.0	1100	812	4.5	3.5	1852		60
11	1896	3.5							
12	2068	3.8							
13	2330	3.8							
14	2439	4.0							
15	2615	4.2	1617	998	5.1	3.3	1543	942	74
16	2954	4.4							
17	3043	4.3							
18	3071	3.9							
19	2897	3.5							
20	3104	3.6	1931	1173	4.4	2.8	1774	1056	157
21	4225	4.8							
22	4657	5.0							
23	5023	5.2							
24	5422	5.5							
25	6007	5.9	4395	1612	8.5	3.2	4100	1453	295
26	6278	6.0							
27	6736	6.3							
28	7235	6.4							
29	7345	6.4							
30	7281	6.2	5565	1716	9.4	3.0	5098	1454	467
31	7178	6.1							
32	7110	6.0							
33	7539	6.0							
34	7690	6.1							
35	8430	6.6	6734	1696	10.5	2.7	6183	1454	551
36	8566	6.7							
37	8785	6.8							
38	8403	6.5	6833	1570	10.5	2.4	6254	1325	579
39	8875	6.8	7206	1669	10.9	2.6	6640	1389	566
40†	8948	6.8	7383	1565	11.2	2.4	6745	1340	638
1941	8864	6.7†							
42	9259	6.9†							
43	9333	7.0†							
44	8765	6.6†					6662	1361	510
45	8958	6.8†							

* Vital Statistics, Bureau of Census, vol. 16, p. 126.

† Forces overseas excluded.

Complete national figures were not available until 1933; until then the rates per 100,000 have more meaning than the actual numbers. In 1900, only 10 states and the District of Columbia were included; after that other states were added gradually until in 1933 all continental U.S. was included.

e between fresh and recurrence cases. This differentiation is neces-
o determine whether the true incidence of ulcer in the population is
asing.

n Sweden since 1918, the incidence of admissions for perforated peptic
in men has definitely increased, whereas it has remained about the
in women (10). This is shown in figure 100, along with the English
s of mortality from peptic ulcer.

n England, Tidy (11) reported on the trends of admissions from 1910
13 at St. Thomas Hospital, London. The general incidence of peptic
in males increased until about 1930, after which it leveled off. The
admissions of females for peptic ulcer declined from 1910 to 1920
to a decrease in the admission of young women under 30 years. Since
, the admissions for peptic ulcer have leveled off. These admission
ds check well with the mortality statistics from peptic ulcer in England.
n the U.S.A., there are no data available to show the trend of admis-
to hospitals for peptic ulcer. The mortality statistics show that the
increased from 2.7 in 1900 to 4.0 in 1910 and 4.2 in 1915 (Table 86).
ing World War I, as in Sweden and England, the rate for males
led off and then declined, as it did in England. After 1920, the increase

Table 87

TRENDS OF MORTALITY FROM GASTRIC AND DUODENAL ULCER
(RATE PER 100,000)*

Ulcer Location	*Period of Years*							
	1911–15	*1921–23*	*1931–33*	*1941–43*	*1911–15*	*1921–23*	*1931–33*	*1941–43*
	Rate				*M:F Ratio*			
nach								
lales	5.5	4.9	6.5	6.7	..	..	..	..
emales	3.2	1.9	1.5	0.9	1.7:1	2.6:1	4.3:1	7.4:1
odenum								
lales	..†	1.8	3.0	3.1	..	..	..	..
emales	..†	0.6	0.5	0.5	..	3.0:1	6.0:1	6.2:1

* Metropolitan Life Insurance Co.

† Prior to 1921 deaths from ulcer of the duodenum were included without segrega-
with those of diarrhea and enteritis. Per cent of deaths from 1911–1935 due to
ric ulcer was 0.38, and to duodenal ulcer from 1921–1935 was 0.14.

Between 1917 and 1920 the death rate for peptic ulcer dropped from 4.5 to 3.3 per
,000. It dropped in Copenhagen, Denmark, and in U.S.A. and English Vital
istics, and it leveled off in Sweden.

in peptic ulcer deaths in males parallels that in England and the inc in admissions in Sweden (Fig. 100) and in hematemesis in Denmark The insured of the Metropolitan Life Insurance Company showe

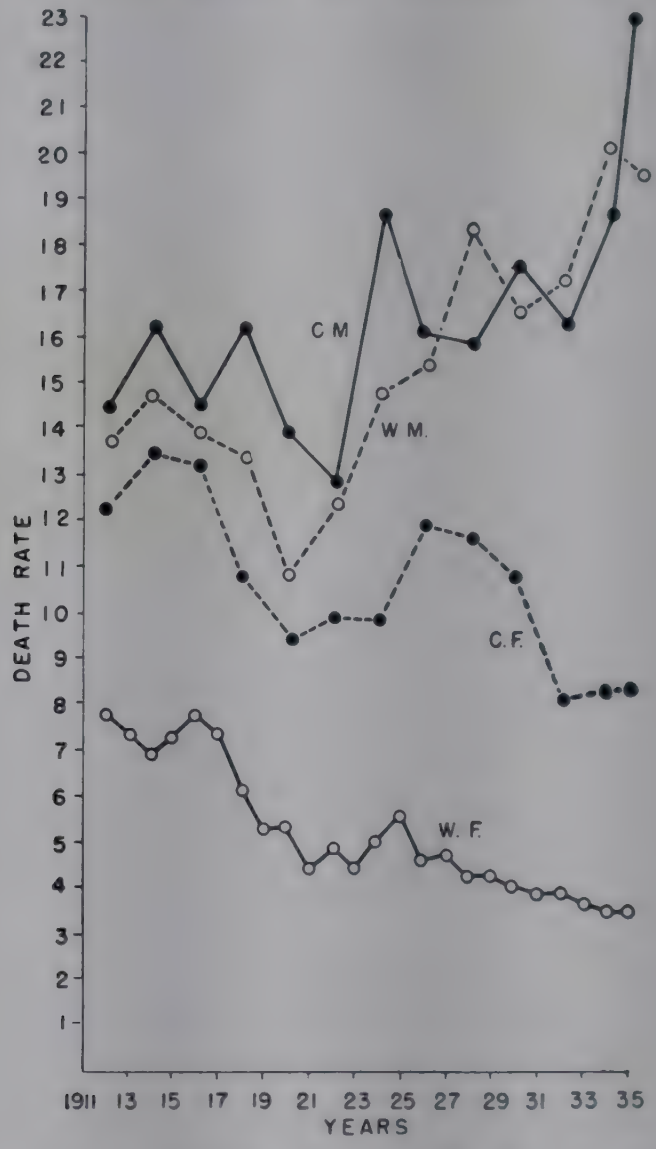


FIG. 101. The changes in mortality rate in white males (*W.M.*), colored males (*C.M.*), white females (*W.F.*), and colored females (*C.F.*) between 1910 and 1935. (Figures taken from *U.S. Census Reports.*)

same trends during World War I (Table 87). The male, female racial changes in the U.S.A. during World War I are shown in figur

It is of much interest that there has been no increase in the deat since 1935 in the United States. The same appears to be true of En except for the heavy air bombardment period.

CHANGES IN CLINICAL INCIDENCE RELATIVE TO SEX OF PATIE AND SITE OF ULCER

Throughout the world, there has been a reported change i clinical incidence of sex and site distribution of peptic ulcer. Th

io of peptic ulcer has changed clinically from 1 M to 3 F to the reverse. the same time, the gastric to duodenal ulcer ratio has changed from or 5 GU:1 DU to at least 3 DU:1 GU (Table 88).

Table 88

SHOWING THE CHANGE WHICH HAS OCCURRED IN THE CLINICAL RATIO OF GASTRIC AND DUODENAL ULCER AND IN THE SEX RATIO*

Author	*No. Cases*	*Ratio M:F*	*Ratio GU:DU*
bert (Bredan 1860–72)	206	1:3.4	..
eenough & Joslin (Boston 1888–98)	187	1:5.2	..
rsløf (Copenhagen 1896–1902)	546	1:5.4	..
sen (Copenhagen 1897–1915)	406	1:1.7	..
ttison (Lund 1910–17)	767	1:1.5	4:1
lmgren (Stockholm 1914–20)	521	1.2:1	..
ery & Monroe (Boston 1913–32)	1435	5.5:1	1:5.4
arncke (Rostak 1922–31)	374	2.5:1	..
lmgren (Stockholm 1921–27)	495	2.5:1	1:1
ang & Chang (Peking 1921–36)	355	2.2:1	1:2
use (Frisco, 1927–37)	575	33:1	1:3
ghman (Johannesburg 1932–36)	245	61:1	1:1.3
iebel & Kunstreich (Warburg 1933–36)	1263	4.6:1	1:2.3
eidinger (Germany 1934–39)	1398	2.8:1	1:1.2
re & Müller (Stockholm 1930–40)	1193	2.5:1	1:3.5

* Ihre and Müller (16).

There are wide variations in these ratios, but we could find no literare since 1920 in which it was reported that peptic ulcer was more equent in the female. However, there are hospital populations today which gastric ulcer occurs more frequently than duodenal ulcer in males and in which gastric ulcer is more frequent than duodenal ulcer 6,27). Tidy (11), at St. Thomas Hospital, London, reported a ratio of astric to duodenal ulcer in females of 3.3:1 in 1933–1936. He also finds ratio of 2.5 GU:1 DU in 1936–1937. The incidence of gastric ulcer mong patients admitted to St. Thomas Hospital was increasing out of roportion to duodenal ulcer. The more recent German statistics (12) ow an incidence of 1 to 1 gastric and duodenal ulcer. The same is true f Switzerland (13).

Tidy (11) points out, as have Morris and Titmuss, that duodenal lcer is more frequent in private practice if the patients are derived from ne high income group or the top social classes. This is supported by the ortality statistics.

It is quite clear from data presented by Bager, Alsted, Hansen, Jenings, Tidy, and Morris and Titmuss that deaths from gastric ulcer in

young women decreased markedly between the turn of the ... World War I and that an increase in duodenal and gastric ul... in men and perhaps some increase in gastric ulcer in wom... years of age.

Present Discrepancy between Clinical Impressions Mortality Statistics Relative to the Frequen... of Gastric and Duodenal Ulcer

It is quite universally believed that clinically duodenal u... common than gastric ulcer. On the contrary, the availab... statistics of every large country indicate that gastric ulcer p... or causes more deaths. For example, the death certificates ... the U.S.A., England, and Sweden show a GU:DU ratio of a... 2.0–2.5 to 1. This is more in line with the more recent patho... of 1 to 1, or 2.5 to 1. The only available recent clinical sta... conform approximately with the mortality and postmort... come from St. Thomas Hospital, London, where the clinical ... gastric ulcer is larger than that of duodenal ulcer. To wh... crepancy between the clinical diagnosis on the one hand a... mortem and certification diagnosis on the other due?

The death certificates are signed and the postmortem ... performed by physicians who, since 1918 at least, have be... the teaching of the leading surgeons and internists of the wo... been taught that clinically duodenal ulcer is more frequent... ulcer. So it can hardly be due to a lack of knowledge o... precepts.

Some would question the accuracy of the diagnoses ... certificates because of the lack of adequate diagnostic inves... the English Army registered, in England and Wales in 1... ulcer deaths, 163 (56 per cent) of which were due to gastr... In the English Army (like the U.S. Army), duodenal ulcer w... three times more frequently (DU:GU = 3.6:1) than gastr...

Jennings (15), in discussing this matter, has expressed ... the accuracy of any statistics on the problem, except those fr... He writes: "diagnosis is too much a matter of fashion. Eve... hospital two radiologists working on the same material ex... varying frequencies of gastric and duodenal ulcer." Here ar... believe that active gastric ulcers are missed in clinical diag... denal ulcers, as scars or small ulcers, are missed in postmort...

The discrepancy may be analyzed as follows: (a) T... clinical incidence of gastric ulcer may be due to the exist... silent gastric ulcers than duodenal ulcers. Madelung (17), in ... report, indicates that more gastric ulcers are "silent" d...

ld be confirmed. Also, small gastric ulcers are more difficult to with the improved radiologic methods for the study of mucosal ures. (b) Small duodenal ulcers and scars may be missed at (c) More duodenal ulcers may be diagnosed than actually occur. duodenitis or superficial erosions which leave no scar may cause s and temporary deformity. Spasm rather than ulcer may cause . A crater is the only true sign of an ulcer. A negative duodenum meaningful of absence of altered function and structure than a stomach, but even this is not conclusive. (d) The clinician's so that more duodenal than gastric ulcer exists may only be true tients he sees, which come from a higher income group or a differential class. There are other factors which must be considered, such ge and sex distribution of the population examined. Sufficient ve been presented to show that patients in charity hospitals, te polyclinics, and in private practice cannot be compared iately.

elieve that the higher incidence of clinical diagnoses of duodenal due, first, to factor *c*, second to *d*, and third to *b*.

A New Type of Ulcer

iscussing the changing incidence of peptic ulcer as indicated by rial, Bager (10) recognized: *first*, the usual type of perforation of nach confined to ulcers on or near the lesser curvature, with a m peak of perforation in males and females of from 50 to 60 years *second*, the acute perforated ulcer of young women, which started ase about the turn of the century and disappeared almost com- about 1910 or 1912; *third*, the usual duodenal perforation; and new type of perforated pyloric ulcer which occurs principally in en and manifests two peaks, one in the early thirties and the other ties. It was the appearance of this new form of ulcer in young ich accounted for the increase in ulcer in men during 1911 to 1930 and accounted, along with an increase in duodenal ulcer, ncreased incidence of peptic ulcer in Sweden, England, and the tates in the face of a decrease in acute perforated ulcer in young Jennings (15) makes a strong case in support of the appearance of type of ulcer by comparing the statistics on perforation by age he statistics being derived from several different sources.

her words, as the acute perforations of ulcers of the body of the in young females relatively disappeared, the incidence of pyloric ric canal and duodenal ulcers increased. This led to an increase verall incidence in perforations, the greatest rise occurring in

have accepted this view so firmly that pyloric and duodenal

ulcers are looked upon as one class and ulcers of the body of the sto and lesser curvature as another class. When this has been done t extent that the pyloric ulcers are not separated from the duodenal as as from the gastric but counted in with duodenal ulcers, as was recently by Knutsen and Selvaag (3), the literature is again being fused and valuable data ruined.

Jennings (15) believes these distal pyloric ulcers are associated annular spasm and should be called spastic perforations.

Ihre and Müller (16) point out that before the modern techniq the examination of the duodenal bulb was introduced in 1921 by lund, juxtapyloric ulcers were viewed as a class by some, a clear distin was not made clinically between the gastric and duodenal locations pathologists did not examine the duodenum closely. This is undoub a contributory factor to the low rate of duodenal ulcer found clinica well as at postmortem; however, it is not a satisfactory explanation the data. Yet, we know of no way of actually proving that the new t ulcer or the "distal pyloric ulcer" did not exist last century, a increase accounts for most of the increase in perforated ulcer.

The natural lag between the appearance of the ulcer and the tin ulcer causes enough distress to cause the patient to see a physician re a study of the epidemiology of the disease more difficult than that of diseases.

Since World War I, Markoff (18) reports what he calls a "new ty ulcer, seen in Switzerland. It is a large lesser curvature gastric associated with low acidity or anacidity. Such an ulcer is not new, ho

Age of Onset of Symptoms from Duodenal and Gastric Ulc

A peptic ulcer may occur at any age, but from the viewpo etiology the average age at which symptoms first occur is of interes agreement from all parts of the world on this point is striking, pr one uses only those reports which deal with a significant number of For example, the average age for the onset of symptoms of duodena in males in Sweden was 32.7 and at the Mayo Clinic, 32.7; for fem Sweden, 33.1 and at the Mayo Clinic, 32.9. The average age for th of symptoms of gastric ulcer in males in Sweden was 41.4 and at the Clinic 40.7; for females in Sweden, 42.8 and at the Mayo Clinic Today, the onset of the symptoms of duodenal ulcer occurs mo quently from 30 to 39 years of age; of gastric ulcer from 40 to 49 y age. The difference in the age at which males and females first d symptoms of duodenal and gastric ulcer is not statistically sign (6, 16) (Table 89).

The duration of symptoms in the United States before the p

Table 89

AGE AT ONSET OF SYMPTOMS OF PATIENTS WHO HAD DUODENAL AND GASTRIC ULCER*

of t of toms	Duodenal Ulcer						Gastric Ulcer					
	All Patients			Operated on			All Patients			Operated on		
	M	F	Total	M	F	Total	M	F	Total	M	F	Total
)	6	0	6	..	..	..	..	..	..	..	..	..
)	72	21	93	2	2	4	4	1	5	..	..	..
)	181	49	230	62	17	79	39	9	48	9	3	12
)	171†	45†	216†	195	45	240	74	11	85	43	2	45
)	76	26	102	160†	49†	209†	62†	14†	76†	92†	22†	114†
)	40	6	46	99	15	124	32	12	44	49	17	66
)	5	3	8	27	12	39	12	3	15	26	6	32
)	..	..	..	6	0	6	..	..	..	4	0	4
tal...	551	150	701	551	150	701	223	50	273	223	50	273
erage age in yrs....	32.7	32.9	32.8	42.7	43.5	42.8	40.7	43.1	14.2	47.8	49.8	48.2

Eusterman and Balfour (6).

Decade into which average age falls.

Duodenal ulcer: Average age of onset of symptoms 33 yrs.
" " " operation 43 yrs.
Gastric ulcer: " " " onset of symptoms 41 yrs.
" " " operation 48 yrs.

Average duration of symptoms in 100 physicians coming to operation was 13 years the average age at operation was 47 years.

Table 90

DURATION OF SYMPTOMS*

Age	0–9	10–19	29	39	49	59	69	70+
es.—No.....	2	124	262	119	91	48	29	1
s. duration.....	0.5	2	11	19	14	16.5	17	20
ales—No.....	0	38	83	110	37	45	9	2
s. duration.....	0	1.5	10.5	13.5	16	19.0	19.5	12

Reported by Dr. J. Friedenwald in 1912 (19).

ulcers are looked upon as one class and ulcers of the body of the stomach and lesser curvature as another class. When this has been done to the extent that the pyloric ulcers are not separated from the duodenal as well as from the gastric but counted in with duodenal ulcers, as was done recently by Knutsen and Selvaag (3), the literature is again being confused and valuable data ruined.

Jennings (15) believes these distal pyloric ulcers are associated with annular spasm and should be called spastic perforations.

Ihre and Müller (16) point out that before the modern technique for the examination of the duodenal bulb was introduced in 1921 by Akerlund, juxtapyloric ulcers were viewed as a class by some, a clear distinction was not made clinically between the gastric and duodenal locations, and pathologists did not examine the duodenum closely. This is undoubtedly a contributory factor to the low rate of duodenal ulcer found clinically as well as at postmortem; however, it is not a satisfactory explanation of all the data. Yet, we know of no way of actually proving that the new type of ulcer or the "distal pyloric ulcer" did not exist last century, and its increase accounts for most of the increase in perforated ulcer.

The natural lag between the appearance of the ulcer and the time the ulcer causes enough distress to cause the patient to see a physician renders a study of the epidemiology of the disease more difficult than that of acute diseases.

Since World War I, Markoff (18) reports what he calls a "new type" of ulcer, seen in Switzerland. It is a large lesser curvature gastric ulcer associated with low acidity or anacidity. Such an ulcer is not new, however.

Age of Onset of Symptoms from Duodenal and Gastric Ulcer

A peptic ulcer may occur at any age, but from the viewpoint of etiology the average age at which symptoms first occur is of interest. The agreement from all parts of the world on this point is striking, provided one uses only those reports which deal with a significant number of cases. For example, the average age for the onset of symptoms of duodenal ulcer in males in Sweden was 32.7 and at the Mayo Clinic, 32.7; for females in Sweden, 33.1 and at the Mayo Clinic, 32.9. The average age for the onset of symptoms of gastric ulcer in males in Sweden was 41.4 and at the Mayo Clinic 40.7; for females in Sweden, 42.8 and at the Mayo Clinic 43.1. Today, the onset of the symptoms of duodenal ulcer occurs most frequently from 30 to 39 years of age; of gastric ulcer from 40 to 49 years of age. The difference in the age at which males and females first develop symptoms of duodenal and gastric ulcer is not statistically significant (6, 16) (Table 89).

The duration of symptoms in the United States before the patients

Table 91

NUMBER OF DEATHS BY SEX FROM PEPTIC ULCER IN U.S.A. FROM 1935–1945 INCLUSIVE

	Under 1 Yr.	*1–9*	*10–14*	*14–19*	*20–24*	*25–29*	*30–34*	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*	*60–64*	*65–69*	*70–74*	*75–79*	*80–84*	*85–89*	*90–94*	*95–99*
1939 Male	8	9	4	33	112	181	299	443	633	858	1002	1013	807	708	497	357	167	53	14	2
1940 Male	10	10	3	22	65	151	236	406	546	754	908	977	799	704	547	334	202	57	8	2
1941 Male	6	3	4	26	65	134	263	321	524	750	976	949	868	705	523	343	179	61	13	3
1942 Male	10	2	0	19	63	131	227	373	503	795	936	1034	950	783	546	381	211	78	14	1
1943 Male	14	8	4	17	52	118	203	357	519	748	974	1029	969	773	622	360	189	83	16	1
1944 Male	10	10	2	18	29	88	199	321	512	724	871	974	917	777	570	366	183	70	13	4
1945 Male	20	4	2	10	36	89	174	320	510	632	907	1009	966	866	584	365	329	75	14	2
M Total	78	46	19	146	422	892	1601	2541	3747	5261	6574	6985	6276	5316	3889	2506	1460	477	92	15
1939 Female	13	5	5	10	28	32	63	93	117	144	147	184	177	183	181	139	97	40	10	1
1940 Female	12	3	4	10	16	27	46	39	71	95	135	125	147	174	150	146	86	41	10	1
1941 Female	4	5	2	4	14	27	37	54	75	101	121	147	144	177	146	123	93	45	12	0
1942 Female	8	5	1	3	14	31	30	41	63	97	117	129	158	181	152	135	115	42	8	2
1943 Female	5	5	3	2	11	23	42	51	81	110	120	140	164	188	174	135	98	38	12	2
1944 Female	7	3	5	0	11	35	41	51	66	90	108	152	169	148	162	136	103	47	13	3
1945 Female	6	2	0	4	11	21	32	51	69	96	116	130	145	189	172	158	76	58	9	0
F Total	55	28	20	33	105	196	291	380	542	733	864	997	1104	1240	1137	972	668	311	74	9
Ratio M:F	1.4	1.6	1.0	4.4	4.0	4.5	5.5	6.7	7.0	7.2	7.6	7.0	5.7	4.3	3.4	2.6	2.2	1.5	1.2	1.6
Per Cent Males	58*	62*	49	81	80	82	84	86	88	88	88	88	85	81	77	72	69	61	55	62
Total M & F	133	74	38	179	527	1088	1892	2921	4289	5994	7438	7982	7380	6556	5026	3478	2128	788	166	24
Death Rate, 1945	1.2	0	0	0.2	0.8	1.5	2.5	4.4	7.1	9.8	14.4	18.2	22.4	27.6	2617	33.3 for 75*				

*The ratio of M:F under one year is 1.4:1; the M:F ratio of total deaths under one year is 1.3:1. The sex difference is not statistically significant until after 14 years of age.

than gastric ulcer, principally because the duodenum has a thinne and is narrower as compared to all parts of the stomach except the p canal. But since there is no significant difference in the delay that pa with gastric and duodenal ulcer show in being admitted to the ho good evidence is lacking. The pyloric or prepyloric ulcer, we feel ca causes the patient to consult the physician early, as in the case of pyloric cancer or tumor, due to obstruction. Until it can be shown duodenal ulcer causes symptoms sooner and that these symptoms the patient to seek hospital admission sooner, the earlier period at duodenal ulcer causes hospital admissions may be used as a point in of duodenal ulcer having a different etiology from gastric ulcer.

Peptic Ulcer Mortality According to Sex and Age

The vital statistics for the U.S.A. from 1939 to 1945 on the rela sex and age to mortality from peptic ulcer have been entered in Tab The graph of the numbers dying in each age group makes a nice shaped, or normal, curve (Fig. 102).

Approximately 40 per cent of the deaths from peptic ulcer occur 60 years of age. The number of deaths due to ulcer per 1

Table 92

Mortality from Peptic Ulcer (Rate per 100,000)*

1911–35 *Gastric ulcer*	*Age Periods*					
	1–20	*20–24*	*25–34*	*35–44*	*45–54*	*55–64*
White males	5.8	1.7	4.4	10.7	16.8	18.8
Females	2.2	1.1	1.7	3.0	4.7	7.1
Colored males	6.5	3.0	5.0	10.8	15.9	22.6
Females	4.7	3.3	4.1	6.2	9.7	15.0
1921–35 *Duodenal ulcer*						
White males	2.6	0.7	2.4	5.1	7.0	7.9
Females	0.5	0.2	0.4	0.9	1.3	1.8
Colored males	1.5	1.1	1.6	2.2	4.6	4.8
Females	0.5	0.3	0.5	0.6	1.4	1.2

* Metropolitan Life Insurance Co.

Death rate increases with age. The death rate in gastric ulcer is higher in males than white males but the death rate for duodenal is higher for whi colored. Death rate for gastric ulcer is higher in colored than white females. T is no difference in regard to duodenal ulcer. See effect of type of work on inc gastric and duodenal ulcer (p. 546).

sons increases with age (Fig. 102). The peak of the number of urs at 55 to 59 years, the age period which is the peak for males. for the number of deaths for females occurs years later at 65 to (Table 92).

TION OF POPULATION DENSITY TO DEATHS FROM PEPTIC ULCER

nly sizable quantity of data available on this subject has been from the mortality statistics in England by Morris and Titmuss presented in Table 93. It will be noted immediately that the

Table 93

ION OF RESIDENCE IN CITY, TOWN, AND COUNTRY TO MORTALITY RATE FROM PEPTIC ULCER (RATES PER 100,000 LIVING)*

land & Wales	20–25		25–35		35–45		45–55		55–65		65–70		70+	
	M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
A. Mortality from Gastric Ulcer														
	1	1	6	1	12	5	36	11	42	16	48	23	40	21
oroughs	2	1	5	2	15	4	27	8	27	10	30	13	26	16
tricts	2	1	4	1	13	3	23	7	25	10	29	15	27	14
tricts	1	1	5	2	10	5	19	7	19	9	24	14	27	11
& Wales	2	1	5	2	14	4	25	8	26	11	30	15	28	15
B. Mortality from Duodenal Ulcer														
	1	0	4	0	8	0	15	4	22	1	25	5	23	5
oroughs	1	0	4	0	9	1	15	2	13	2	16	2	15	4
tricts	1	0	4	0	8	1	12	1	14	2	14	3	14	4
tricts	1	0	2	0	6	0	9	2	11	2	17	3	12	3
& Wales	1	0	3	0	8	0	13	2	14	2	16	3	15	4

ris and Titmuss (14).

35 the death rate from gastric ulcer for London is considerably in excess of ther geographic areas for both gastric and duodenal ulcer in men and

te from gastric ulcer in London is considerably larger than in ions. After 35 years of age, it is twice that in the rural population. king to note how deaths from both gastric and duodenal ulcer with population density, as indicated by looking down each olumn in the table. Men living in London at an age of 45 to 55

have a higher death rate from peptic ulcer than men at an age of 65 t 70 living in the country.

Social Class and Mortality from Peptic Ulcer and Cancer

In England it is possible to study the relation of social class to th incidence of disease. The social classes are defined approximately a follows:

Class 1. Leading professions, wealthy independents, directors an managers in certain finance and insurance companies (2.5 pe cent).

Class 2. Employers and managers in mining, industry, transpor retail, and wholesale trades, lower professions and commerci employees in a few occupations carrying a measure of ind pendence (14.0 per cent).

Class 3. Skilled workers, salesmen, shop assistants, and clerical worke (49.2 per cent).

Class 4. Semiskilled workers and agricultural laborers (17.8 per cen

Class 5. Unskilled workers (16.5 per cent).

Table 94

Effect of Social Factors on Mortality from Peptic Ulcer (1930–32)*

Males: Gastric Ulcer	*Age Group*						
	20–25	*25–35*	*35–45*	*45–55*	*55–65*	*65–70*	*70*
	Rate per 100,000 Living						
1 & 2 (Professional & Business)	1	3	8	17	24	37	
3 (Skilled Workers)	2	4	12	25	31	32	
4 (Semiskilled Workers)	2	6	15	27	29	28	
5 (Unskilled Workers)	2	8	19	31	31	27	
Males: Duodenal Ulcer							
1 & 2	1	3	6	13	19	24	
3	1	3	7	13	15	18	
4	2	4	8	11	13	14	
5	1	4	9	14	14	13	

* Morris and Titmuss (14).

Morris and Titmuss (14) have presented data showing that the de rate from gastric ulcer is higher among the males of the lower inc

groups until the age of 55 years, after which the males of the higher income group have a higher rate. The males of the lower income group show the same death rate as those of the higher income group from duodenal ulcer until the age of 55, after which the males of the higher income group have a higher rate (Table 94). Heupke (22) also finds that the incidence of gastric ulcer and gastritis is higher among unskilled laborers than among more skilled craftsmen.

Table 95

MORTALITY AMONG WOMEN FROM PEPTIC ULCER IN RELATION TO SOCIAL CLASS*†

Class	*Married Women*	*All Men*	*Single Women*
1	53	72	80
2	98	87	..
3	99	101	123‡
4	99	102	..
5	118	118	..

* From Morris & Titmuss (14).

† All classes = 100 at ages 35–65 (1930–1932).

‡ 74 per cent of single women were in class 3 occupations and most were under 35 years of age.

The death rate from peptic ulcer among the married women of the high income group is remarkably low (Table 95). Unmarried women, when they assume the responsibility of skilled workers, show a high death rate from peptic ulcer. The married women in the low income group, the wives of unskilled workers, have as high a rate as their husbands.

Morris and Titmuss (14) report that they have data showing "that unemployment or enforced leisure led to a reduction in ulcer mortality; but when unemployment declined after pronounced depression, mortality rose sharply. A return to work, but perhaps very insecure re-employment, meant more ulcer deaths." Data supporting such an observation would be of etiologic significance.

Ihre and Müller (16), in studying the relation of occupation to the incidence of peptic ulcer in Sweden, found traveling salesmen, tram car and railroad employees, and sailors significantly more frequently affected.

A definite relation appears to exist also between *the incidence of cancer* and the *income class*. Thus, gastric ulcer and gastric cancer are similar in

this regard, and gastric irritation by chemical, caloric, and mechanical means may predispose to or provoke both diseases (14) (Tables 96, 97).

Table 96

CANCER OF STOMACH, DEATH RATE PER MILLION (ENGLAND & WALES)*

Sex	Period	Age								
		Under 25	25–35	35–45	45–55	55–65	65–75	75–85	85+	Ages Standardized
M	1911–20	1	18	98	367	967	1737	1795	1017	186.4
	21–30	1	22	116	413	1087	2074	2407	1708	221.1
	31–35	1	22	118	432	1092	2234	2731	2055	232.1
F	1911–20	1	15	76	261	678	1296	1542	1146	139
	21–30	1	15	75	259	696	1522	2027	1786	155.
	31–35	1	18	73	238	657	1555	2303	2120	155.

* Morris and Titmuss (14).

Table 97

SOCIAL CLASS AND CANCER OF THE STOMACH
ENGLAND AND WALES DEATH RATE PER MILLION (1930–32)*

Social Class	Ages 45–55			Ages 55–65		
	Men	Married Women	Single Women	Men	Married Women	Sing Wo
1. Professions and wealthy	254	172	203	609	475	40
2. Managers	335	..	..	950	..	..
3. Skilled workers	423	252	285	1076	663	74
4. Semiskilled	456	259	271	1257	659	78
5. Unskilled	536	299	..	1324	767	105

* Morris and Titmuss (14).

EFFECT OF MARITAL STATE ON MORTALITY FROM PEPTIC ULCER

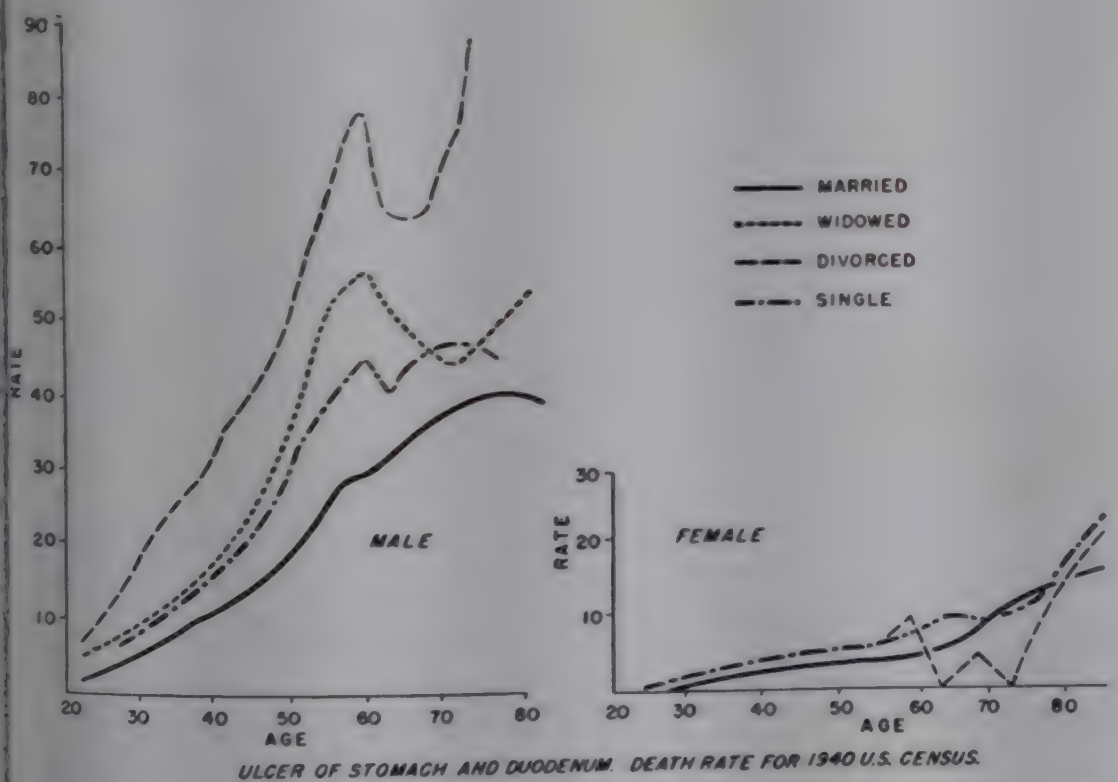
In Table 98 are shown data on the distribution of deaths from pe ulcer in relation to the marital state and age. The rate is graphed aga age in Fig. 103. This study of the U.S. Bureau of Vital Statistics yi some most interesting results (23). First, it shows that peptic ulc primarily an affliction of males and that the marital status does not sig cantly affect the peptic ulcer death rate of females. The highest (Fig. 103) is for divorced males; the lowest for married ones. The rat

Table 98

MORTALITY FROM PEPTIC ULCER ACCORDING TO MARITAL STATUS

Ulcer-Stomach & Duodenum	*Total 8948*	*Single 1448*	*Married 5570*	*Widowed 1533*	*Divorced 300*	*Not Stated 97*
Under 20	95	79	5	..	..	1
20–24	123	78	42	..	1	2
25–34	571	205	334	9	21	2
35–44	1259	239	895	46	60	19
45–54	2129	315	1541	160	92	21
55–59	1194	163	794	177	52	8
60–64	994	120	651	188	26	14
65–69	934	105	584	220	20	5
70–74	733	75	409	226	15	8
75–79	494	36	211	237	6	4
80–84	296	23	86	179	6	2
85+	122	8	20	90	1	3
Not stated	9	2	4	1	0	2

* U. S. Bureau of the Census, 1940.



103. Death rate from ulcer at various ages according to marital status and sex. (Figures taken from *U.S. Census Reports.*)

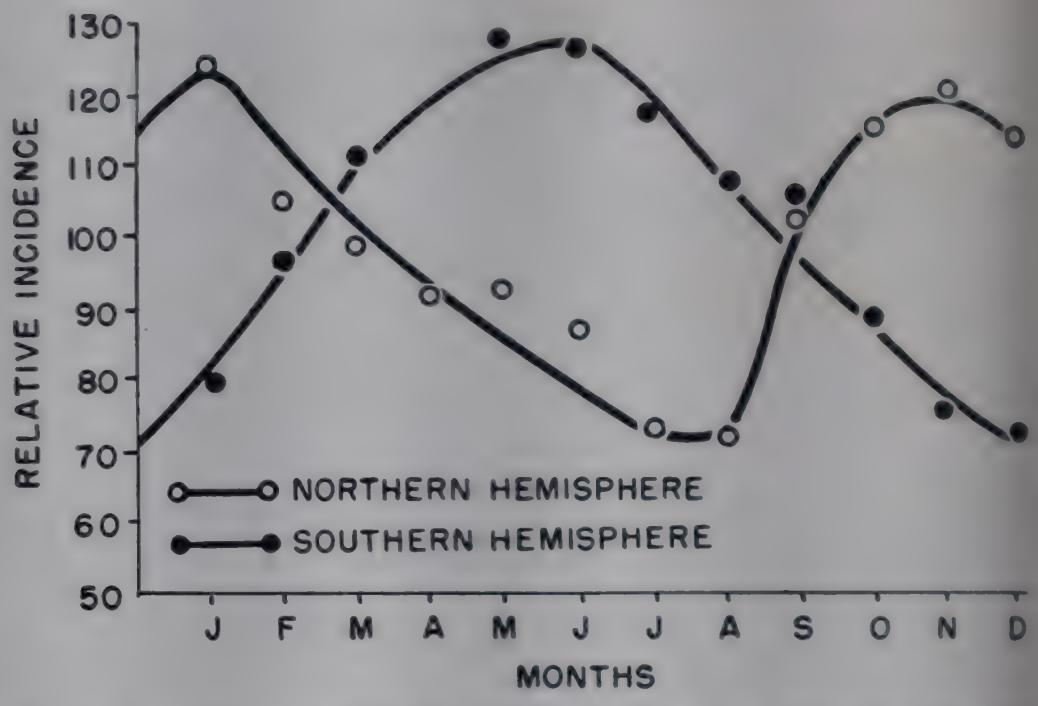


FIG. 104. Relative incidence of peptic ulcer in the northern and south hemispheres during the months of the year.

widowers is only slightly higher than that for bachelors in the age grou under 54 years, but rapidly rises after 54 years of age.

All curves show a jog upwards at the age of 55 to 59, the increase be most pronounced for divorced and widowed males and least marked married males. There is an increased risk of males with peptic ulcer dy if they are not married. This risk is greater for divorced males than widowers and bachelors. The risk is greatly increased for divorced m and widowers during the age period of 55 to 59.

It is interesting that exopthalmic goiter is the only other disease t is analogous to peptic ulcer in its relations to marital status.

RELATION OF INCIDENCE OF PEPTIC ULCER TO MONTHS OF YEAR

The relation of the time of the year has been referred to under discussions of perforation, hemorrhage, and mortality (p. 549).

Mattison (24) presents data on the time of onset of recurrences Albrecht (25) on the time of roentgen diagnosis. Albrecht's data are few to show a significant change except a low incidence in July August. Mattison's data show significant peaks in October, Noven and January (Table 99).

Linn (26) has provided long-needed data on the effect of seaso the incidence of symptoms of peptic ulcer from the Southern hemisp A peak in May and June is evident but the cases are too few to statistical significance (Table 100 and Fig. 104).

Table 99

MONTHS OF ONSET OF SYMPTOMS

	Month											
	J	*F*	*M*	*A*	*M*	*J*	*J*	*A*	*S*	*O*	*N*	*D*
tison (24)	197	165	139	149	151	129	130	112	175	195	171	194
echt (25)	42	34	36	21	22	36	19	18	23	31	43	32
d (66)	33	34	44	33	34	28	13	29	32	28	52	25
otal	272	233	219	203	207	193	162	159	230	254	266	251

Table 100

SHOWING THE INCIDENCE OF THE ONSET OF SYMPTOMS BY MONTHS IN AUSTRALIA*

	Months											
	J	*F*	*M*	*A*	*M*	*J*	*J*	*A*	*S*	*O*	*N*	*D*
al	51	61	71	59	80	81	75	68	66	56	49	46
	15	19	21	10	35	28	25	20	20	23	18	21
	36	42	50	49	45	53	50	48	46	33	31	25

* Linn (26).

EFFECT OF HEAVY AIR RAIDS AND WAR ON INCIDENCE OF AND MORTALITY FROM PEPTIC ULCER

Morris and Titmuss (14) have studied the apparent effect of air raids the mortality from peptic ulcer in England. The effect of the air raids he Fall of 1940 is apparent in Tables 101 and 102. Deaths from both tric and duodenal ulcer increased among both males and females, but ticularly among males. This is of considerable value because the death from peptic ulcer was quite uniform from 1927 to 1938 in England. will be noted that the people in the rural areas were also affected as raids spread from London to the country towns.

The effect of the early stages of the war on the incidence of peptic r in Germany is definite; this is also evident for the population of tzerland.

In Germany at the Krupp works in Essen, the observations made on incidence of ulcer during the early part of the War by Rothe (27) are wn in Table 103. In Berlin, Kalk (28) reported the data given in

Table 104. In Switzerland, Markoff (18) reported an increase in a surve of 41 hospitals as is shown by the data in Table 105.

Table 101

HEAVY AIR RAIDS AND MORTALITY FROM PEPTIC ULCER AS RELATED TO SEX AND TO SITE OF THE ULCER*

Year	*Males*				*Females*			
	1st Qt.	*2nd Qt.*	*3rd Qt.*	*4th Qt.*	*1st Qt.*	*2nd Qt.*	*3rd Qt.*	*4th Qt.*
1939	1109	929	905	973	342	246	250	278
40	1272	991	1003	1259†	366	279	290	364†
41	1384†	1312	876	884	378†	298	209	257
42	1181	892	770	940	317	238	185	225
	Gastric Ulcer				*Duodenal Ulcer*			
1939	999	799	814	871	452	376	341	380
40	1107	838	862	1086†	541	432	431	537†
41	1695†	1048†	680	755	581†	562†	405	386
42	978	702	608	761	520	428	347	404

* Morris and Titmuss (14).

† Effect of raids more pronounced on males and on gastric ulcer as regards mortality.

Table 102

EFFECT OF AIR RAIDS ON LONDON AND REST OF ENGLAND AND WALES*

Year	*London*		*Rest of England and Wales*	
	Males	*Females*	*Males*	*Females*
1939	483	150	3433	966
40†	638 (+32%)	185 (+23%)	3805 (+11%)	1114 (+15%)
41†	478 (− 1%)	134 (−11%)	3855 (+12%)	1007 (+ 4%)
42	392 (−19%)	99 (−34%)	3306 (− 4%)	865 (−10%)

* Morris and Titmuss (14).

† Air Raids of fall of 1940 and winter of 1941.

Kretchmar (13) and Markoff both find that the increase of peptic in Switzerland was due to an increase in new cases as well as recurr in old cases. It is interesting that Markoff attributes the increase in p ulcer to nervous tension and that Kretchmar attributes it to the relat low protein and high vegetable roughage diet. Kretchmar's pa

amed the diet and he agreed because the increase did not occur until 41–1942, when the fear of invasion had subsided.

*Table 103**

INCIDENCE OF ULCER IN GERMANY DURING EACH PART OF WORLD WAR II

Year	*Examinations for Dyspepsia*	*Positive for Ulcer*	*DU*	*GU*
1937–38	2142	449 (20.9%)	266	58
1938–39	2509	644 (25.6%)	409	56
1939–40	2837	822 (31.0%)	407	154

* Rothe (27).

*Table 104**

INCREASE IN INCIDENCE OF ULCER IN GERMANY DURING WORLD WAR II

	Total Patients	*Gastritis*	*Peptic Ulcer*	*DU*	*GU*
Months before the War	3663	1.8%	4.7%	3.2%	1.5%
Months of War	3541	4.1%	12.2%	6.3%	5.9%

* Kalk (28).

*Table 105**

INCREASE IN INCIDENCE OF VARIOUS DISEASES IN SWITZERLAND DURING WORLD WAR II

	1937–39	*1940–42*	*Increase*	*Per Cent*
Total sickness	223,841	245,332	21,491	9.5
Gastroduodenal ulcer	3,131	4,093	962	30.7
Gastric ulcer	1,376	1,895	519	37.7
Duodenal ulcer	1,421	1,821	400	28.1
Chronic gastritis	1,153	1,203	50	4.3
Gastric cancer	1,763	1,878	115	6.5
Gastric perforations	305	411	106	34.7
Gastric ulcer bleeding	161	200	39	24.2

* Markoff (18).

ENVIRONMENTAL FACTORS SUSPECTED OF CAUSING ONSET OF PEPTIC ULCER AND ITS RECURRENCES

This subject has been referred to in previous chapters in this part the book and will be dealt with again in the next two chapters. We all refer here only to those factors which have been studied by question-

ing the patient relative to events which may have been causally to the onset or recurrence of disease.

When this was done by Emery and Monroe (29) in a series patients, no cause could be assigned in 40 per cent or 520 patients was assigned in 26 per cent or 334 cases; emotional disturban assigned in 20 per cent or 258 cases; and upper respiratory infec 13 per cent or 167 cases. Davies and Wilson (30) found difficult finances, working conditions, or illness of others assigned as events recurrences in 80 per cent of 52 recurrences in 53 patients. T found that finances, working conditions, and other social difficul assigned as causes of the onset of ulcer symptoms in 84 per cent of 2 patients. Using hernia patients as controls, only 22 per cent a some environmental difficulty with the condition. Later, the same (31) interrogated 50 patients who bled from their ulcer 58 m 25 patients whose ulcer had perforated. Of the 75 patients, 65, cent, traced the onset of the perforation or hemorrhage to difficu finances, working conditions, or illness of relatives. Most of those not trace their recurrence or the onset of their disease to some event gave a history of having been under emotional tension or a long time. The absence of upper respiratory infections from th noteworthy, particularly in view of the literature prior to 1925, theory of focal infection, which claimed cures for ulcer after remo and related the onset of ulcer to dental, tonsilar, and sinus infect in fashion.

Nicol (32) studied 232 ulcer patients (187 DU and 45 GU) a an external strain assigned as a cause in 70 per cent of the cases. cent, the strain was mental; in 23 per cent, physical; and in 54 unknown. The physical strains included dietetic errors, physi respiratory infections, excessive smoking, and miscellaneous i difficulty with such an approach is that the patient may re reading that mental strain or overwork is supposed to predispos ulcer. The same may have applied to the patients of Emery an when questioned at a time foci of infection was being publi possible cause of peptic ulcer.

Davies and Wilson (30), however, interrogated 175 pa hernia and only 22 per cent gave a history of financial and s culties. They also compared the personality types of the pa hernia and peptic ulcer by the Culpin scale. (This scale is d measure tensions and compulsive tendencies.) Eighty per c ulcer patients showed tensions and compulsive tendencies. In only 15 per cent of the hernia patients.

Chalkley (33) reports a similar observation made under

ere, however, less favorable for drawing conclusions. He had patients who were doing well under management for peptic ulcer . were on the relief roll. They were notified that on a certain date allotments would be discontinued. Thirty-nine of the 50 patients within 10 to 14 days with a recurrence of symptoms. The acidity increased and 11 had to be hospitalized. They failed to to therapy and after two or three weeks were told that their t would be resumed. Within 48 to 72 hours evidence of marked mprovement occurred. Unfortunately, this was not accompanied ntrol group on relief who were receiving an allotment for some ease.

yone who has had experience with a large group of ulcer patients the psychic factors mentioned above apparently induce a recur- n the contrary, however, recurrences also occur without evidence ic trauma or any other exciting cause. A hemorrhage or perfora- y come "out of a clear sky." Nevertheless, it is easier to provide at the present time for the view that conflicts and tension serve ng causes than any other factor in the environment, except per- dietary indiscretions by those patients who are on management e not definitely entered a remission.

chmar (13), who reported an increase in new cases of peptic ulcer erland during World War II, on questioning the patients found y ascribed their difficulty most commonly to the rough, high- e-cellulose diet. He points out that the increase did not occur in d 1940 when the people in Switzerland feared invasion, but in d 1942 when the diet had to be markedly changed.

tically every author discussing the subject of environmental rentions worry, dietary indiscretions, excessive smoking, alcohol, reats, and overwork. It is interesting that Bardod's English pa- nked cold and damp weather first before worry as a cause of d recurrences of symptoms.

Relation of Other Diseases to Peptic Ulcer

ad of recognizing peptic ulcer as a disease entity *per se*, many have d that peptic ulcer occurs secondary to other diseases. There is a rman literature on this subject, almost entirely conjectural. It particularly the relation of cardiovascular, pulmonary (tuber- thyroid, renal, colonic, cholecystic, and appendiceal disease. ationships were rejected by most of the pathologists. The re- lationship of cholecystic and appendiceal disease was frequently ed by Moynihan, Deaver, and Judd. This old literature is ade- reviewed by Redwitz (34).

Appendicitis and Cholecystitis

Several authors in the United States have been sufficiently impressed by the association of cholecystic and appendiceal disease and peptic ulcer to present considerable data on the subject (7, 35–37). The data have been collected and are presented in Table 106. They show that there is significantly greater association of appendicitis and cholecystitis with duodenal ulcer than with gastric ulcer.

Table 106

Showing that Appendicitis and Cholecystitis Are More Commonly Associated with Duodenal than with Gastric Ulcer*

Additional Lesion Found at Operation	*Surgically Verified*			
	Duodenal Ulcer		*Gastric Ulcer*	
		Per Cent		*Per Cent*
Appendicitis	363 cases	51.8	146 cases	38.9
No appendicitis	337 cases	48.2	229 cases	61.1
$\chi^2 = 16.1$				
Cholecystic disease	169 cases	10.3	64 cases	6.3
No cholecystic disease	1471 cases	89.7	957 cases	93.7
$\chi^2 = 12.6$				

* References 35, 36, and 37.

This association with peptic ulcer as regards appendicitis was found by Rössle (38) from a postmortem material in which the ratio of gastric to duodenal ulcer was 6 to 1, which does not check with the clinical observations cited in Table 106. The correlation observed may be fortuitous and due to the fact that the incidence of disease of the appendix and of gallbladder and the chronic sequelae are high, and that in the American data the incidence of duodenal ulcer is high and in the German data that of gastric ulcer is high. For example, what is needed to test this correlation is a control group without peptic ulcer so that the incidence of appendicitis and cholecystitis in non-ulcer patients could be known. In Rössle's autopsy series he had such a control, but his observations have not been confirmed.

The apparent significant correlation of duodenal ulcer with appendicitis and cholecystitis rather than with gastric ulcer is meaningful only if there is some causal relationship. If such a causal relationship did exist

ould either increase the incidence of duodenal ulcer or decrease the ncidence of gastric ulcer. The only evidence of a relationship between he appendix and gallbladder on the one hand and the duodenum on the ther, except for reflex effects, is an anatomic one, namely, a lymphatic onnection (39,40). It is known that distension of the appendix and gall-ladder may reflexly cause pylorospasm or decrease in gastric tone and eristalsis, depending on the nature of the stimulus. The lymphatic onnection would predispose to associated infection in the case of duo-enal ulcer and reflex disturbances which would cause motor disturbances, rimarily of the pylorus and stomach. Appendicitis or cholecystitis can-ot have a specific etiologic relation to duodenal or gastric ulcer because lcer in both sites may develop after appendectomy or cholecystectomy.

Hepatitis is frequently associated with cholecystitis; no information is vailable on appendicitis. This is mentioned because hepatitis is associated ith the occurrence of spontaneous peptic ulcer in dogs.

The absence of any direct relation between acute appendicitis and eptic ulcer is indicated by the fact that the mortality from appendicitis n the U.S. is decidedly increased during the summer months when the ortality from peptic ulcer is definitely lowest.

Oral Sepsis

In view of the observations of Rosenow and the great importance ttributed to the role of foci of infection as a cause of various acute and hronic diseases, especially peptic ulcer, it is surprising that there have ot been a number of studies of the incidence of peptic ulcer in patients ith and without oral sepsis. We have been able to find only one such tudy, which was made by Hurst (41). The data are recorded in Table 107. nfortunately, the age and sex distribution of the "normal controls" and f the patients with oral sepsis is not given, so one cannot determine hether the two groups are homogeneous. If the two groups are homo-eneous, then two remarkable conclusions are warranted. One is that ral sepsis markedly predisposes to but does not cause peptic ulcer. The ther is that this is true of pyorrhea alveolaris and not of apical infections. However, we are inclined to be very skeptical regarding the homogeneity f the two groups studied by Hurst and Spencer-Payne. This study should e repeated.

Upper Respiratory Infections and Tonsillitis

Emery and Monroe (29) found that 13 per cent of 1279 recurrences ight be attributed to upper respiratory infections. We have found no imilarly large series of patients in which an attempt was made to find a ontributory cause of recurrences. Although there is a tremendous

clinical literature on the relation of foci of infection to peptic ulcer, w have found no article which presents controlled data similar to those c Spencer-Payne's on oral sepsis so that its statistical significance at leas may be determined.

Table 107

INCIDENCE OF DENTAL DISEASE IN PEPTIC ULCER PATIENTS AS COMPARED TO NON-PEPTIC ULCER PATIENTS*

	No. Cases	*1*	*2*	*Both 1 and 2*	*1 + 2 + 3*		*Endentulous*		*Sound Tee*	
		Pyorrh. Alv.	*Apic. Inf.*		*Total*	*Per Cent*	*Total*	*Per Cent*	*Total*	*Pe Ce*
Gastric ulcer	25	7	6	6	19	63	4	13	7	2
Duodenal ulcer	126	32	11	50	93	74	10†	8	23	1
Anastomotic ulcer	36	20	2	6	28	78	6	17	2	
Total ulcer	187	59	19	62	140	74	20	10	32	1
"Normal" controls	102	11	24	18	53	47	0	..	49	4

1 = Pyorrhea alveolaris; 2 = Apical infection.

* Hurst and Stewart (41).

† "At least 3 out of these 10 had residual infections in the jaws. N.B." As none the "normal" controls were edentulous, the percentages have been reduced to allow the 10 per cent endentulous among ulcer cases.

TOTAL DENTAL DISEASE

	Bad Teeth	*Sound Teeth*	*Total*
Ulcer cases	140	32	172
Controls	53	49	102
Total	193	81	274

$\chi^2 = 26+$.

APICAL INFECTIONS ONLY

	Apical Infect.	*Sound Teeth*	*Total*
Ulcer cases	19	32	51
Controls	24	49	73
Total	43	81	124

$\chi^2 = 2.4$; insignificant but in favor of apical infections.

PYORRHEA ONLY

	P.A.	*Sound Teeth*	T
Ulcer cases	59	32	
Controls	11	49	
Total	70	81	1

$\chi^2 = 28$.

RELATION OF ACTIVITY OF AN ULCER TO PRESENCE OF BACTERIA IN ITS MARGINS AND BASE

In relation to recurrences associated with an infection, Duval a his colleagues (42) have reported that when an ulcer is excised during asymptomatic period no signs of infection and acute inflammation found; the reverse is true if the ulcer is excised during a symptom period. This study should be repeated.

Cirrhosis of the Liver

Peptic ulcer has been reported to occur in cirrhosis of the liver in man (43). Its incidence at autopsy in connection with cirrhosis is 2 per cent or less (44).

Schnitker and Haas (45) have reported a slightly greater incidence of cirrhotic changes in the liver of ulcer patients than in controls. A slight increase in the blood lipase (olive oil splitting lipase) of patients with peptic ulcer has been observed by Jergesen and Simonds (46).

Diabetes Mellitus

The incidence of peptic ulcer in diabetes mellitus has been discussed by Joslin (47) and Wilder (48). Joslin states that he failed to see a case of peptic ulcer in his first 2700 cases of diabetes. Wilder saw an incidence of 61 cases or 2.3 per cent of peptic ulcer in 2584 diabetics during 1935–1937 inclusive. In the same period (1937), the incidence of peptic ulcer in other patients at the Mayo Clinic was 3.5 per cent. This shows that peptic ulcer is not increased in diabetes.

Marble (49) in collected series found that the incidence of achlorhydria was 32.8 per cent in 399 diabetics. The usual incidence of achlorhydria in patients above 40 years is 10 to 15 per cent. However, to make such a comparison patients in the same age groups should be used.

We cannot conclude from the evidence available that the diabetic is less susceptible to peptic ulcer, though he is certainly not more susceptible. This is significant because hyperinsulinism stimulates gastric secretion and might predispose to ulcer.

It has been reported that, because of the prevalance of achlorhydria in diabetes, atypical ulcer histories as regards pain are frequent (50).

Cardiovascular Disease

Organic Disease. Statistical postmortem studies have been made, particularly by Hauser's students, on the relation of valvular incompetency of the heart to peptic ulcer. The results show that passive congestion is not a factor (34, 44). The interpretation of the autopsy findings relative to the role that arteriosclerosis plays varies. The large literature on this subject is discussed by Hauser (44) and Redwitz (34).

Because so many ulcer patients die in the arteriosclerotic age group, a direct relation between arteriosclerosis of the gastric and duodenal arteries and an ulcer in the arteriosclerotic patient has neither been proved nor disproved. Cases of isolated and generalized sclerosis of the gastric vessels have been reported with and without ulcer. When ulcer does occur with local sclerosis of the gastric or duodenal arteries, one cannot

deny that the sclerosis predisposed to the formation of the ulcer by decreasing the local blood supply due to small emboli or to stiffening o the arterioles in the mucosa. It could not reasonably be due to an infarc tion of a large vessel because they may be tied without causing an ulcer

On the contrary, many ulcers are found at autopsy or in surgica specimens with intact blood vessels beyond the base and margins of th ulcer where the wall of the vessels is exposed to the injurious action of acid This and the fact that the incidence of peptic ulcer is not high in the ol age group indicates that arteriosclerosis, even in the aged, plays only minor etiologic role, if any.

Functional Disease. *Angiospastic or Vasoneurotic Diathesis.* Some autho who have suggested that peptic ulcer is due to a disturbance of the veg tative nervous system have looked for evidence of overactivity either i the secretory or motor systems. When good evidence of a clear-c overactivity of the vagus nerves was not found, attention was directe to the vasomotor nerves of the sympathetic division. It was suggeste that localized vasospasm was the cause of ulcer.

Mueller and Heimberger (51) have reported that when examined b capillary microscopy the capillaries of the vasoneurotic person have bizarre form or pattern quite different from that of the normal perso They examined specimens of freshly resected mucosa. The capillari were irregular in their course and caliber, being constricted in places a dilated in others. The changes were not correlated with the age or t degree of acidity of the patient and the presence of gastritis. The conditi was present in the gastric mucosa of patients with duodenal ulcer but w less marked. Most specimens from patients with gastric cancer w normal. This has been confirmed histologically and by capillary micr copy (52, 53). Mayer-List (54) has reported that the same capill abnormality may be detected in the lips of ulcer patients. Mueller belie that the capillary abnormality decreased the resistance of the mucosa damaging influences. It is believed that this subject is worthy of furth investigation, in view of the irregularities of the capillaries reported occur in schizophrenics.

Association of Polycythemia and Peptic Ulcer

Isolated reports on the coexistence of these two disease entities e in the literature (55, 56). However, the only satisfactory study availa is that of Wilbur and Ochsner (57) of the Mayo Clinic. These obser collected 143 cases of polycythemia vera, of which 29 had had suffici gastrointestinal complaints to warrant x-ray study. Twelve of these, 8 per cent of the total, were found to have evidence of peptic ulcerati Ten had duodenal ulcers; two had gastric ulcers. Peptic ulcers in a con group of 200 patients with hypertension occurred in 2 per cent,

3.2 per cent in the total clinic population. This difference would seem o be statistically significant. The association is of further interest in that he known tendency of the polycythemic patient to vascular thrombosis nay play a part in the pathogenesis of ulcer in these patients. That is, hrombi may form in the capillaries of the mucosa and produce an area of owered resistance to digestion.

Spastic or Dyskinetic Colon

After the introduction of the concept of imbalance of the autonomic ervous system by Eppinger and Hess, peptic ulcer, because of the tend-ncy to find hypernormal acidity of the gastric contents, hypermotility, nd pylorospasm, was placed in the vagotonic category. Rössle (58) ssumed a reflex disturbance of the vagus and Holler (59) postulated an rganic disease of the vagus. Bergmann (60) proposed that the vagus auses the initial lesion by causing a spasm of the musculature and keeps he lesion chronic by affecting motility so as to augment mechanical rritation of the ulcer.

"Spastic constipation," or the spastic or dyskinetic colon, was looked pon by some as a manifestation of parasympathetic neurotic stigmata, y others as a part of the total picture of peptic ulcer, and by others as a esult of the ulcer. Thaysen (61) viewed spastic constipation as a gastro-enic reflex. Ruhmann (62) found constipation of some type present in 0 per cent of his patients with peptic ulcer. "Spastic constipation" riginated with or after the onset of ulcer distress; in one third of his atients "atonic constipation" followed the onset of the ulcer. Hurst (41) tates that constipation is frequently present in ulcer patients; it is in-reased in severity by recurrences and may disappear entirely during emissions. Without doubt, "constipation" is an outstanding complaint f the ulcer patient and as a result some patients produce bowel dysfunc-ion with cathartics. But there is no good evidence proving that "spastic onstipation" is a symptom of peptic ulcer or a part of the picture or erhaps a sequel of therapy. It is well known that it may occur without lcer, but we have no data showing whether it has a higher or lower ncidence in the ulcer patient than in the general population. If a psy-hosomatic factor involving motor function is concerned in producing olonic dyskinesia or "spastic constipation," it would seem reasonable to uppose that the mechanism concerned should also affect the motor ctivity of the stomach or duodenum in some persons.

Chlorosis

It has been suggested that peptic ulcer may have been the cause of hlorosis. Chlorosis is a disease of young women in which the blood picture esembles that due to iron deficiency or chronic blood loss. It was specifi-

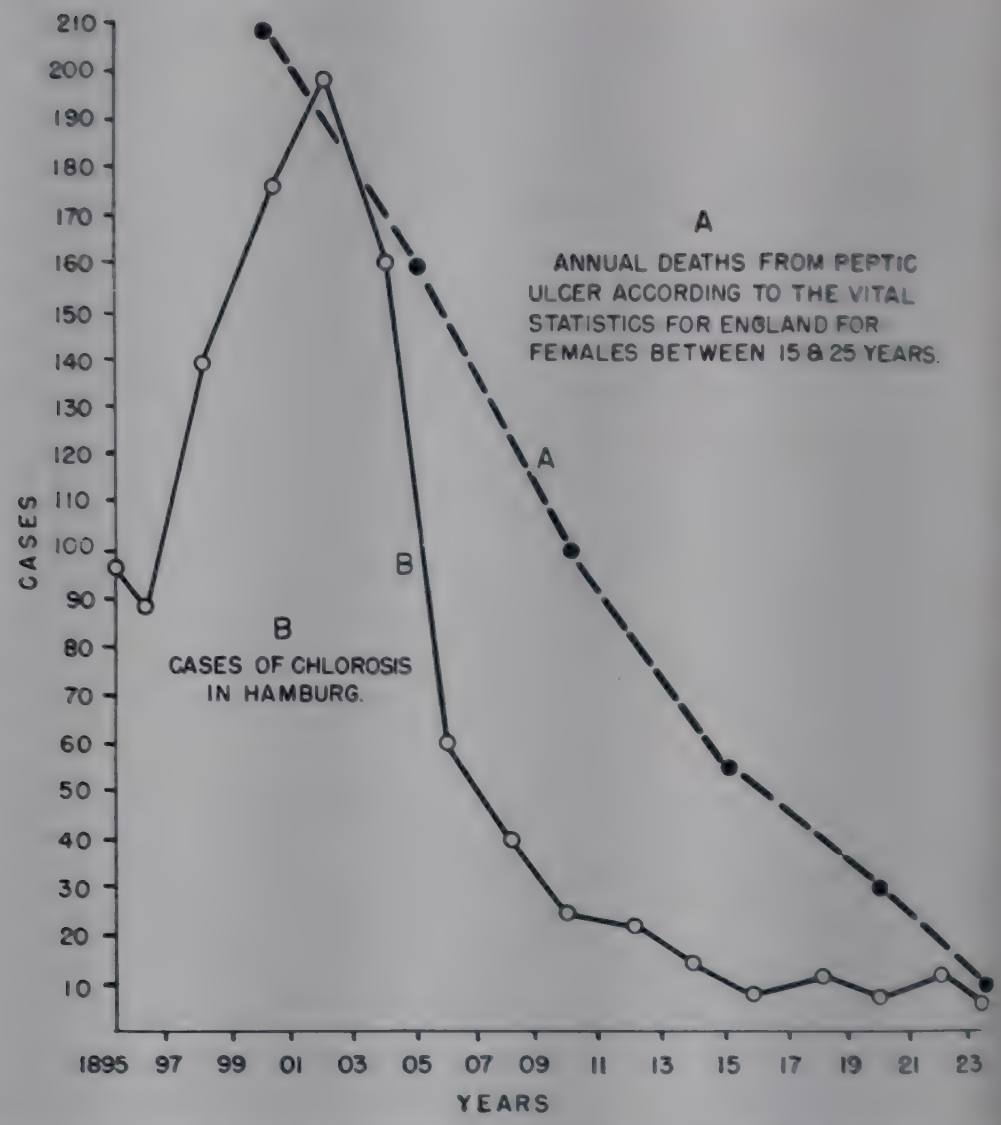


FIG. 105. Showing the relationship between the number of deaths from pe ulcer in females in England and the incidence of chlorosis in Hamburg betw the years 1895 and 1923. (Data from Jennings: *Lancet*, **1**:395, 444, 1940.)

cally treated by iron administration (Blaud's Pills). The incidence of disease increased during the latter part of the 19th century, reache peak about 1900, and then practically disappeared.

Osterspey (63) in 1892 suggested that chlorosis was due to blee from peptic ulcer. Hyperacidity was looked upon as one of the constant symptoms of chlorosis by Riegel (64) in 1887, and Osswald in 1894. It is also interesting that at the time when the hemoglobinom and hemocytometer came in as a fashion the routine was to determin hemoglobin and if low to give Blaud's Pills. The iron would darke stools and mask melena or chronic blood loss from an ulcer. Stolte has reported that he later found gastric ulcer in patients in whor diagnosis of chlorosis had previously been made.

The curves showing the decrease in incidence of chlorosis an

th rate from gastric ulcer of young women under 25 years of age ncide quite strikingly. The curve of the increase in tight lacing and n its discontinuance also coincides (Figure 105). This warrants the formance of experiments on animals to determine whether external striction of the stomach will cause gastric ulcer and constriction of the ist will cause anemia due to some other effect than chronic blood loss m a peptic ulcer.

Constitutional Factor in Peptic Ulcer

Introduction

The existence of constitutional factors which are responsible for iations in the response of different species and individuals to the same nulus is a basic biologic fact. So, to state that a constitutional susceptiity to peptic ulcer exists is to state a biologic truism. However, like so ny basic facts in biology, the causal mechanisms are still to be learned. When susceptibility of an organism or one of its parts to an injurious nt is studied, different grades of susceptibility are always found to st. A "dose" of the injurious agent, of course, may be found which will ure the most resistant. We are certain that if an adequate quantity of 6 per cent hydrochloric acid were continuously dripped into any nan stomach a duodenal ulcer would develop in time. But, as was nd in our experiments on dogs, the duodenum of some humans would velop the ulcer much sooner than others. This analogy between man and g is appropriate for the following reasons: the susceptibility of the unum to acid is greater than that of the stomach and duodenum; acid he chief cause of jejunal ulcer in the dog; and after gastroenterostomy n and dog develop ulcer in the jejunum in approximately the same centage of cases (10 to 25 per cent).

A constitutional factor of susceptibility to disease will determine what tion of the individuals in a group will develop the disease as well as the ency of the etiologic agent or agents which cause the disease.

Since it is unlikely that the constitutional factor or factors will change hin two or three generations in a mixed population, the study of nges in the incidence of a disease should reveal environmental inences of etiologic and potential prophylactic value.

The best evidence, and we believe it is crucial evidence, demonstrating individual constitutional susceptibility of what we call the "ulcerceptible patient" is the remarkable tendency of ulcer to recur in the ne individual. The constitutional factor in peptic ulcer has been studied several ways. These will be referred to only very briefly.

Hereditary Transmission of Ulcer

The literature up to 1933 has been reviewed by Riecker (68). We find, as in the case of other chronic diseases, so-called "ulcer families" (69, 70). In addition, patients have been questioned, with the result that ulcer, gastric cancer, and nervous dyspepsia are found to occur more often in families of ulcer patients than non-ulcer patients according to some authors but not according to other authors. It should be added that the best work shows a positive correlation. Reports that identical twins residing in different geographic locations have developed peptic ulcer at about the same time are to be found (71). An instance of dizygotic twins is reported in which perforation occurred in each within an hour of one another (71). We believe that hereditary predisposition probably exists but do not believe that its existence has been established by the evidence submitted to date.

Racial Susceptibility to Ulcer

The Chinese at one time were thought to be nonsusceptible to peptic ulcer. It was then shown that the Chinese in Peiping were just as susceptible as Europeans. We now have an excellent autopsy report showing that the Chinese in Java are more susceptible to gastric ulcer than the Javanese, though the latter have a higher gastric acidity (72). A confirmatory study with a closer study of environmental factors, such as the relation to social class and the temperature at which food is consumed is desirable.

Similarly, at one time it was thought that the negro was not susceptible to peptic ulcer. On the contrary, under the same environment he apparently is as susceptible as the white man (73).

Causal Mechanisms of High Susceptibility to Peptic Ulcer

These, of course, could be structural or physiologic.

The structure of the stomach and duodenum relative to the quality and quantity of its mucous cells and Brunner's glands may be inferior, there may be more acid secreting cells than normal. The shape and position of the stomach may be concerned. The mode of insertion of the ligamentous attachments of the stomach and duodenum or the structure of the capillaries may be concerned.

On the other hand, the reflex and autacoidal control of the mechanism for the secretion of acid-pepsin or the secretion of protective secretion may be concerned, so that excessive acid is secreted in response to ordinary stimulus either by lack of balance of excitatory and inhibi

nervous reflexes, or by a lack of balance of hormones which stimulate and chalones which inhibit secretion.

The anatomy and physiology of the mechanisms may be normal, but the training or emotional experience of the individual (personality type) may be such as to lead to an overaction of the reflex mechanisms involved in the control of: (a) acid secretion (an aggressive factor) so that excessive acid is produced continuously; or (b) the secretion of the protective juices (a defensive factor) so that, for example, Brunner's secretion is not adequately formed; or (c) the blood flow through the mucosa (a defensive factor) so that the mucosa is underprotected as regards nutritive materials for repair of cells and alkali for the neutralization of acid as it penetrates the cell.

The healing mechanism of the cells of the gastric and duodenal mucosa may be inherently defective because of there being too little growth and repair promoting substance released in response to injury. The cells of the stomach and duodenum of the ulcer-susceptible person may need more of some dietary principle for their growth and repair, or for the manufacture of mucus and Brunner's gland secretion. The various suggestions made in the literature will be briefly mentioned.

Anatomic Suggestions. At one time it was believed that ptosis of the stomach constituted the constitutional factor. This was given up when it was found that most adults have a J-shaped or vertical stomach and that ulcer occurs in patients regardless of the form or position of the stomach. The J-shaped or hook-shaped stomach was thought to be uniformly characteristic of the asthenic habitus or body form of the ulcer-susceptible person. When it was thought that the occurrence of chronic gastritis was directly related to the cause of gastric ulcer, chronic gastritis was thought to be an evidence of constitutional gastric inferiority. The presence of islands of intestinal glands in the lesser curvature has been considered to be another evidence of constitutional inferiority (p. 516). The rudimentary nature of the magenstrasse or lesser curvature has been referred to as a constitutional factor even though all persons anatomically possess a lesser curvature, though probably not a physiologically functioning gastric passage (p. 515). Structurally, abnormal capillaries in the gastric mucosa of the ulcer patient have been looked upon as a constitutional manifestation.

Physiologic Suggestions. Physiologically, it has been suggested that ulcer patients have a vasoneurotic or angiospastic diathesis (p. 636), a myospastic diathesis or a tendency to spasm of the gastric and duodenal musculature (p. 194), a personality type (p. 664), a low alkaline reserve in the blood (p. 219), and a super-acid secretion (p. 692).

None of these factors have been established as playing a primary role in the genesis of peptic ulcer. We only feel certain that the secretion of some acid is necessary for ulcer formation (p. 765).

Body Build or Habitus and Peptic Ulcer

A great deal of work has been done on the subject of the relation of body build to the predisposition to certain diseases, an idea that was originally based on an easily confirmed fact; namely, that some diseases have an effect on body build. Most of the anthropometric data gathered on this subject, which were reviewed up to 1926 by Redwitz (34) and in 1935 by Feigenbaum and Howat (74), when graphed will show slight differences. These differences, however, when analyzed statistically are found to have no true significance in such diseases as rheumatic fever peptic ulcer, diabetes, cholecystitis, and rheumatoid arthritis (74). That is, by making anthropometric measurements, one cannot predict with any degree of accuracy that a person is predisposed to peptic ulcer.

Hypersthenic and Hyposthenic Gastric Diathesis

Hurst (41, 75) has suggested that on the basis of heredity 80 per cent of persons have a stomach which is capable of dealing with ordinary environmental conditions without sustaining injury. Of the remaining 20 per cent, 10 per cent manifest hypo- or achlorhydria and its associated diseases and the other 10 per cent hyperchlorhydria and its associated diseases. He refers (41) to persons with hyperchlorhydria and a short high horizontal stomach with active peristalsis and evacuation as having a "hypersthenic gastric diathesis" and to those with a hypochlorhydria and a long, low hanging, hook-shaped stomach with slow peristalsis and evacuation as having a "hyposthenic gastric diathesis." He claims that duodenal ulcer is associated with the short stomach and lesser curvature gastric ulcer with the long stomach. Redwitz (34) and others also state that gastric ulcer most frequently occurs in the long, hook-shaped stomach. But we have been unable to find any data showing the relative frequency of duodenal and gastric ulcer in association with a short and a long stomach in a significant series of patients to deny or to support the claim.

Difference in Sex Incidence

A difference in the overall sex incidence of peptic ulcer undoubtedly exists. The difference becomes very definite after the age of 14 years and hence will be discussed in the next section. It should be noted here, however, that if it does exist it may be due to an environmental rather than a constitutional factor.

Peptic Ulcer in Infants and Children in Relation to the Question of a Constitutional Factor

Peptic ulcer in infants and children is an important topic for several reasons.* First, if a constitutional factor exists, it should be evident in newborn infants at an age when many environmental factors such as anxiety, fear, insecurity, and financial and social difficulties do not operate. Second, the secretion of acid by the stomach is at a low ebb in the stomach of the premature or newborn infant, infants under one year, and children under nine years.

Types of Ulcer in Infants and Children. The types of ulcer which occur in infants and children should be considered in relation to the types seen in adults. Three types of ulcer are generally recognized in infants and children.

The *first type* is found within the first two weeks after birth. It is an acute ulcer, usually single, and frequently accounts for the symptom of melena neonatorum (77), which may or may not cause death. If death occurs, sometimes the stomach or duodenum must be carefully examined before and after fixation to find a small penetrating ulcer. If death does not occur, the ulcer may obviously heal by scar formation with or without causing obstruction. Less frequently, the ulcer perforates. This type of ulcer has occurred and perforated in premature infants (78, 79). It has been seen rather frequently in newborn, normal term infants within the first two weeks (80, 81). It has occurred and caused death as early as 24 to 48 hours after birth. In some instances, the pathologic evidence has been of such a circumstantial nature as to lead to the diagnosis of "perforated peptic ulcer *in utero*" (82). In one of these cases, prepyloric obstruction was present and the gastric contents were acid. Similar information is lacking in the other reports.

The *second type* occurs between the first two weeks and the end of the first year. It is also acute or subacute in type. In one instance, they have occurred with sufficient frequency to cause the suspicion that they were due to a specific infection (83). These ulcers generally occur in infants who appear to be well nourished and should be differentiated from those cases of gastroduodenitis found at postmortem in children dying from acute infectious diseases, tuberculous meningitis, congenital syphilis, nephritis, skin burns, and marasmic states.

The *third type* occurs from one to nine years of age and is "chronic" in type. They usually fail to cause the symptoms characteristic of peptic

* The older literature on the occurrence of peptic ulcer in infants is reviewed by Redwitz (34) and the more recent literature by Bird, Limper, and Mayer (76).

ulcer in the adult, which do not occur until 10 or 12 years of age (77). This is one reason why peptic ulcer is so infrequently diagnosed in young children. For example, Procter (80) found that 16 out of 1000 gastric ulcer patients and 26 out of 1000 duodenal ulcer patients dated the onset of their ulcer symptoms to childhood, some as early as three and four years of age.

Frequency of Peptic Ulcer in Infants and Children. As just indicated, the frequency is probably greater than indicated by the figures to follow.

Clinically. Proctor (80), at the Mayo Clinic, reported one gastric ulcer in a child among 1596 adult gastric ulcer patients, and one duodenal ulcer in a child among 6664 adult duodenal ulcer patients.

At Autopsy. The incidence under one year and under 12 years of age approximates 1 per cent of peptic ulcer, if ulcers due to skin burns, tuberculosis, syphilis, and cachexia are excluded (84, 85). A total of between 200 and 300 are recorded in the literature in children under 10 years, but with such incompleteness that the data cannot be used in all cases.

Site of the Ulcer. If pyloric ulcers are included with duodenal ulcers, the ratio of duodenal-pyloric ulcers to gastric ulcer is 2 to 1 in the newborn and 3 to 1 throughout infancy and childhood (76). If pyloric ulcers are classified as gastric, the ratio is approximately 1 to 1. Most of the gastric ulcers are located in relation to the lesser curvature, even in the newborn; most of the duodenal ulcers which perforate are located on the anterior wall (80), as in the adult, and most which bleed on the posterior wall (86), though relatively few authors provide the exact site.

Complications. The complications seen in the adult are seen in infants and children (Table 108).

Table 108

Types of Ulcer Reported in Various Age Groups*

Age	*Stenosis*	*Perforation*	*Bleeding*	*Persistent Pain*	*Total*
0–14 da.	1	18	22	1	42
15 da.–1 yr.	8	15	25	6	54
2–6 yr.	2	3	10	5	20
7–11 yr.	18	15	8	16	57
12–15 yr.	31	26	3	12	72
Total.	60	77	68	40	245

* Bird, Limper, and Mayer (76).

Anastomotic Ulcer. Seventy per cent of the patients between seven and 15 years of age reported in the series of Bird and his associates were operated upon. Most were operated upon for either stenosis (53 cases) or perforation (43 cases), and only a few for hemorrhage (12 cases) and persistent pain (11 cases). Simple closure (37 cases), pyloroplasty and gastroenterostomy (55 cases), and resection (17 cases) were the operations performed, with a total mortality of 11 per cent. At least five cases of anastomotic ulcer have been reported (76, 87).

Theories of Cause of Ulcer in Infants

All the various theories of ulcer genesis have been used to explain peptic ulcer in infants, though no emphasis has been placed on the acid theory.

Some have suggested that ulcer in the newborn is due to retrograde thrombosis from the umbilical stump, or even emboli therefrom which have passed through a still patent foramen ovale. But thrombi are not usually seen in the margins or base of these ulcers. Some have suggested that venous back pressure with congestion of the mucosa and digestion of hemorrhagic areas is concerned. Brain injury resulting from a birth injury has been believed to be a cause. However, evidence of brain injury was found in only one of nine cases of peptic ulcer of infants autopsied at Cook County Hospital, Chicago (88). Most of their cases of peptic ulcer in newborns were in infants who had been delivered without anesthesia or the aid of instrumentation. Similarly, Guthrie (86) failed to find evidence of brain lesions in her cases, all of which experienced normal deliveries. It is not easy to explain these ulcers on an infectious basis because it is unusual to find any evidence of inflammation in the margin of these ulcers. Local angiospasm as well as myospasm has been suggested. Some of these children are described as being "poor feeders" and have lost considerable weight from vomiting by the time they die. In those infants who have suffered a prolonged course of malnutrition, the ulcer may be analogous to those found in malnourished protein-deficient animals.

The occurrence of peptic ulcer in the newborn and the infant under one year is exceedingly interesting from the viewpoint of pathogenesis because of the low acidity of the gastric contents found in most instances. Yet free acid can be found in the stomach of infants as early as the first and second days of age and is even found in premature infants. Miller (89) found it present in all but six of 50 breast fed infants during the first week after birth. Nevertheless, the acidity of the gastric contents does not reach adult proportions until after six months or more of age. Unfortunately, the acidity of the gastric contents has been tested in only two cases according to our search (82, 90). However, it is known that gastric and duodenal ulcer does occur occasionally in patients with low acidity (91). This shows

that the principal factor in such cases is a decrease in local resistance digestion and a defect in the mechanism of the repair of injury.

On the Sex Ratio of Peptic Ulcer in Infants and Children and Its Significance

We have not been able to demonstrate a clearly significant differen in the sex ratio of peptic ulcer until after 10 to 15 years of age. If o refers to Table 109, compiled by Bird and his associates, it will be fou that more males than females have peptic ulcer. When one refers to t

Table 109

Sex Incidence of Peptic Ulcer in Infants and Children*

Age	*No. Ulcer Deaths*		*Adding Successive Years*		*Ratio M:F*
	M	*F*	*M*	*F*	
0–2 weeks	15	11	15	11	1.36:1
2 wk.–1 yr	22	15	37†	26†	1.4:1
2–6 yr	11	9	48	35	1.4:1
7–11 yr	35	22	83	57	1.5:1
12–15 yr	43	23	126	80	..
Total	126	80	..	..	1.5:1

* Bird, Limper and Mayer (76).

† If Polson's 5 males and 6 females which died of ulcer under 1 year are added, the totals become 42:32 or 1.31:1. The ratio of all M to F deaths under one year in the U.S. is 1.3:1.

119 of these patients were operated on and 124 were verified by autopsy or x-ray.

table prepared by Sandweiss and his associates (92), it will be fo that the cases under one year are too few and that in the more nume group of children up to 12 years the males predominate. Inspectio Table 91 giving the deaths in the United States of infants and chil from peptic ulcer for the years 1939–1945 inclusive will show tha sex ratio for infants and children under 14 years of age ranges 1.0 M:1.0 F to 1.4 M:1.0 F. The mortality statistics from Eng (Table 110) under 10 years show a sex ratio of deaths from peptic of 1.15:1. None of these differences can be considered statistically si cant. This is especially true in view of the fact that more males females are born and that more males than females die of all ca particularly during the first year of life. The sex ratio of deaths fro

causes during the first year is approximately 1.4 M:1 F in the U.S. and 1.3 M:1 F in England.

Table 110

DEATHS OF MALE AND FEMALE INFANTS AND CHILDREN FROM PEPTIC ULCER AND ALL CAUSES IN ENGLAND (1927–37)*

Age Period	*Ulcer Deaths No. Cases*			*Deaths Not Due to Ulcer*	
	M	*F*	*Ratio M:F*	*Age Period*	*Ratio M:F*
0–1 yr	14	13	1.08 :1		
1–5 yr	6	9	0.665:1	0–5 yr.	1.294:1
Total	20	22	1.1 :1	5–10 yr.	1.15 :1
5–10 yrs	11	5	2.2 :1		
Total	31	27	1.15 :1		
10–15 yr	17	9	1.89 :1	10–15 yr.	1.065:1
15–20 yr	146	59	2.48 :1	15–20 yr.	0.976:1

*Data taken from The Registrar-general's Statistical Review of England and Wales for the Years 1927 to 1937, vols. 7 to 16, New Annual Series, London, H. M. Stationer's Office.

After puberty, the number of male deaths over female deaths from peptic ulcer increase from a ratio of 4.4:1 at 14 to 19 years of age to 7.6:1 at 50 to 54 years of age, after which the ratio rapidly declines to that which obtained in childhood.

It is well known that male deaths from all causes decidedly predominate over female deaths *in utero*, under the first year, and up to the fourteenth year. This is the hereditary susceptibility of the male to disease and injury which is true of most animal species. Twenty-five per cent more males died under the diagnosis of peptic ulcer under one year of age in the U.S. during 1939–1945, and 25 per cent more died of dysentery and enteritis, which is the third ranking cause of death. If the apparent higher incidence of peptic ulcer in males should prove to be significant on the compilation of a larger number of cases, as we suspect it will, it would reflect only the almost universal biologic law (which also applies to the alimentary tract) that the male is more susceptible to disease during infancy. If the difference should prove not to be significant, it would indicate to us that the biologic law does not apply to peptic ulcer.

With the onset of puberty, however, some factor operates to increase decisively the clinical incidence and the death rate of the male from gastric and duodenal ulcer in most populations. Mind you, we do not say to influence the susceptibility of the male or female to peptic ulcer. On the basis of the evidence with which we have just dealt, the susceptibility may be the same after puberty as it was before.

The increase in incidence in the male after puberty may be due either to an increase in susceptibility or to an increase in exposure to ulcerogenic factors in his environment. An increase in the clinical incidence and deaths from peptic ulcer also occurs in the female, the chief difference being that the increase is greater in the male.

The greater incidence in the male could be due to a greater exposure of the male to ulcerogenic exogenous environmental factors. Social custom encourages or compels the male to become aggressive and the female submissive in behavior. This possibility is supported by evidence showing that women in the skilled and unskilled laboring class have as high a death rate as men (Table 95). Some exogenous factor, possibly tight lacing, unequivocally operated before 1900 to cause females under 30 years of age to develop gastric ulcer.

The male hormone may operate to increase gastric secretion. It is known that average acidity of the Ewald test-meal is definitely greater in the male than female between the years of 20 and 50. The female hormone may operate to inhibit secretion. The male hormone may render the mucosa of the stomach and duodenum more susceptible to injury, as suggested by Sandweiss and his associates. This view is supported by the fact that women with peptic ulcer usually enter a remission during pregnancy and that something is present in the urine of pregnant women which has a favorable effect in preventing and promoting healing in peptic ulcer in M-W dogs. This substance, however, may not be a sex hormone; it may be a growth or repair promoting substance, present in normal urine and increased in pregnancy urine (anti-ulcer substance) (p. 445).

There is really only one quite well established difference between the physiology of the male and female relative to the difference in the sex incidence of peptic ulcer. It is that the male on the average secretes more acid.

Conclusion

It must be confessed that we do not know what disturbed anatomic or physiologic mechanisms in the ulcer-susceptible person render him or her more susceptible to those environmental factors which cause the onset and recurrences of the disease. That is, we cannot measure any function or

group of functions and predict that a person is ulcer-susceptible and will develop ulcer under certain environmental conditions. We thought that we might do it with the caffeine test-meal, but it has not worked (p. 398).

On the Identity of Gastric and Duodenal Ulcers

Throughout this study "peptic ulcer" has been used to describe both gastric and duodenal ulceration. At the same time, differences between gastric ulcer and duodenal ulcer have been pointed out. It is appropriate, therefore, to consider the evidence for and against the identity of ulcer in these two sites.

Experimental Evidence. If we begin with evidence derived from the experimental production of ulceration, certain differences are immediately apparent. Cinchophen and caffeine in the cat, bilateral vagotomy in the dog and rabbit, protein deficiency in the dog, starvation and calcium deficiency in the rat, all produce ulceration of the stomach characteristically. Skin burns, the excessive secretion of acid (especially that induced by histamine), external biliary fistulae, biliary and pancreatic duct obstruction, and instillation of acid into the stomach all produce ulceration of the duodenum primarily. But it should be immediately added that, with the exception of the "vagotomy" ulcer, all these experimental ulcerogenic procedures tend to produce ulcers in both locations, although predominantly as listed above.

As a rough summary, it would seem that in these experimental ulcers acid plays a greater role in the duodenal ones, and mechanical factors such as stasis play a greater role in the gastric ones. However, it should be kept in mind that all the acid of the stomach must go over the pylorus and duodenum, a relatively narrow area, and not as much acid strikes the lesser curvature.

Although the cinchophen ulcers reported in man have been gastric, the protein-deficiency gastric ulcer in dog does not find a counterpart in man. The South Indian data on low protein diet seems to indicate that duodenal ulcer is formed more frequently than gastric, although both occur.

Anatomic Evidence. Some anatomic evidence on the relative poverty of the blood supply to the lesser curvature, prepyloric, pyloric, and duodenal areas might tend to explain similarities of response to ulcerogenic procedures, but this does not provide strong evidence that gastric and duodenal ulcer are identical. However, the two types of erosions described by Langerhans and Aschoff, (a) the fundus erosions and (b) the erosions of the gastric pathway, would tend to separate ulcers of the body of the stomach, which heal rapidly, from ulcer of the pyloroduodenal area.

Evidence from Pathologic Physiology. Certain bits of evidence

from the pathologic physiology of these ulcers seem to distinguish ga
from duodenal ulceration. Typically, basal, nocturnal, and stimula
gastric secretion is either normal or less than normal in gastric ul
Further, there is no augmentation of motility in gastric ulcer. On
other hand, all phases of secretion and motility tend to be increased a
the normal in duodenal ulcer. Ulcers of the prepylorus or the pyloric c
are more like the duodenal than gastric as far as associated secretio
motility is concerned. These disturbances of function, however, should
as has often been done, be assumed to be proof of a difference in etio
Theoretically, they may all be secondary to the occurrence of the
and represent differences of response of the secretory and motor me
nisms to differently located ulcers. More evidence, involving studie
gastric and duodenal ulcer patients during remissions as well as exac
tions, than we now possess is required.

Some *pathologic evidence* would tend to separate these two typ
ulcers. Gastric ulcer never or very rarely extends into the duode
however acute ulcers of the stomach and duodenum occasionally co
and chronic ulcer may affect both organs as frequently as 6 to 14 pe
of cases. Gastric ulcer has a greater tendency to undergo malignant
formations. Here, too, this last feature does not *per se* mean that g
ulcer is different from duodenal ulcer. It may merely represent the
ence in potentiality of the soil on which the ulcer is planted, or
mechanical irritation is more carcinogenic in the stomach than che
irritation. Thus, the difference in size of duodenal and gastric
duodenal being considerably smaller than gastric, may represent
vidual differences rather than differences of the disease entities.

Clinical Evidence. Certain clinical observations seem to poin
difference between gastric and duodenal ulcer. A family history
to be twice as common for patients with duodenal ulcer. Gastric
occurs more frequently in the laboring and low-income groups; duo
ulcer more often in the more prosperous, managerial, and intel
professions.

The lower age of onset of symptoms in duodenal ulcer (30 to 4
be compared with the peak at 40 to 50 in patients with gastric ulce
is consistent with autopsy and mortality statistics, which show the g
number of gastric ulcers at 50 years and over, while the peak of inc
of duodenal ulcers is in the third and fourth decades.

The significance of the changing incidence of ulcer at the vario
in both sexes is not entirely clear in relation to the light that th
throw on the identity or lack of identity of the two types of ulcer

If we leave aside for the moment the decline in ratios of G
in females, which is probably related to a specific environmenta

iscussed before (p. 638), there has been an overall increase in the ber of duodenal ulcers in both sexes, although more marked in the s, with no such definite trend in the overall frequency of gastric r. This disparity offers only a thin thread of evidence that the two rs are different entities. The sexual and racial differences do not ide evidence for or against the similarity of the two types of ulceration. Seasonal recurrences may be more characteristic of duodenal than ric ulcer, as some suggest, but the evidence is inadequate to establish a difference. The best evidence fails to indicate any difference.

The higher tendency to perforate, which is reported to be characteristic uodenal ulcer, does not necessarily represent more than local anatomic rences, and the evidence would seem to indicate that the increased ency to perforate related to the increase in wartime stress and strain lted in an increase in *both duodenal and gastric* ulcer.

The higher mortality from bleeding gastric ulcer may represent only older age group involved. This does not explain the higher frequency leeding gastric ulcer.

The somewhat higher number of anastomotic ulcers that follow roenterostomy for duodenal ulcer than follow gastroenterostomy for ric ulcer is probably related to the higher levels of gastric acid secretion e duodenal variety. It is also of interest that, while occasionally a new ric ulcer may occur following gastroenterostomy for duodenal ulcer, have been unable to find a single case where a duodenal ulcer has cared following gastroenterostomy for gastric ulcer.

Despite these differences, however, the similarities between gastric duodenal ulcer are very marked. The gross appearance of the lesions, wing for differences of anatomic location, the symptoms, the life ory of the individuals with the disease, the complications and sequelae, responses to surgical and medical therapy, all point to a fundamental tity between gastric and duodenal ulcer. The differences are probably e related to local factors.

Summary

. The data on clinical incidence are confined to limited populations are of limited value as bases for conclusions. For most populations, following estimates are reasonable. From 5 to 10 per cent of the people lop an ulcer during a lifetime. The total incidence of those actively cted above the age of 20 at any annual survey varies from 1 to 3 per . From 0.15 to 0.38 per cent above the age of 20 years require hos- lization annually.

Throughout the world, there has been a rise in the incidence of ulcer. has been attributed by some to such factors as improved technic of

examination, but there is much convincing evidence that the incidence of peptic ulcer has actually increased.

The clinical incidence of peptic ulcer has changed from 1 M:3 F to the reverse since 1900. Although there are wide variations in the reported ratios, there have been no reports since 1915 that ulcer was more frequent in the female. At the same time, the ratio of gastric to duodenal ulcer has changed from 4 to 5 GU:1 DU to at least 3 DU:1 GU.

Although the clinical incidence of duodenal ulcer is reported to be higher than that of gastric ulcer, there are more deaths reported from gastric than duodenal ulcer. This is true of almost every report except some from hospitals in London and Switzerland, where the clinical reports check well with mortality statistics and autopsy statistics of approximately 1:1. This discrepancy may be contributed to by: (a) the misinterpretation of duodenal deformity and irritability as being due to ulcer rather than to duodenitis; (b) difference in clinical material, especially in regard to social class; (c) the missing of small duodenal ulcers and scars at autopsy and (d) the difficulty in the diagnosis of small gastric lesions. The appearance of a "new type" of ulcer, a distal pyloric lesion occurring particularly in young men, seems to account for some of the changes in incidence.

Data on the average age of onset of ulcer symptoms are in general agreement. In the case of duodenal ulcer, the onset occurs most frequently from 30 to 39 years of age, and in gastric ulcer from 40 to 49, with no important sex difference.

Approximately 40 per cent of deaths from ulcer occur above 60 years of age, the peak being from 55 to 59 years of age for males, and 10 years later for females. The death rate increases with age.

Mortality data from England reveal a direct correlation between deaths from peptic ulcer and population density. They also show that the death rate from gastric and duodenal ulcer is related to social class. In the United States, mortality data show that the death rate is not related to the marital state of females but that it is higher among the divorced, widowed, and single males. The death rate is particularly high for divorced and widowed males between 50 and 60 years of age.

Some evidence is available indicating that tensions created by financial, employment, and domestic difficulties are overtly related to the onset of the first and subsequent attacks of the disease. This has not been established with an adequate amount of control data. Acceptable evidence from Switzerland shows that the incidence of new cases of ulcer increased during the war as well as the incidence of recurrences and complications. One author ascribes the increase to nervous tension; another to a relatively low protein, high roughage-vegetable diet.

II. There is a large volume of literature on the relation of other ases to peptic ulcer. The belief once advanced that peptic ulcer was ndary to, or occurred concomitant with, appendicitis and chole- itis was based on inadequate control data. The same is true for oral is, upper respiratory infections, arteriosclerosis, colonic dyskinesia or stic constipation," and chlorosis. Further observations are indicated the relation of oral sepsis and the claim that the capillaries in the ach and lips of the ulcer patient are abnormal.

III. The existence of variations in susceptibility among different viduals or the same individual is a biologic fact. There is no good on to doubt that some individuals are more susceptible to peptic r than others; if this were not so, it would be a unique biologic nomenon. The nature of this constitutional susceptibility has not been ned; that is, there is no measurement or set of measurements excluding x-ray and anamnesis, which, when applied to a group consisting of a ure of 100 persons with and 100 persons without peptic ulcer, will t the ulcer group and will have no more than 15 per cent error.

The various constitutional factors which have been suggested to be erned have been discussed.

The sex difference, which has existed now since 1910–1915, has no in explanation at present.

Peptic ulcer in the newborn and the infant is of theoretic importance use presumably environmental factors operate to a lesser extent than e adult and because gastric acidity is low.

Both clinical and mortality statistics show that male deaths from ic ulcer between one year and 10 years predominate in a ratio of M:1 F. This, however, is the rate of male deaths to female deaths from auses, including deaths from dysentery and enteritis, and is an expres- of the basic biologic law that males are more susceptible than females isease in general, the cause of which is unknown. At puberty under ronmental conditions existing since 1900–1910, decidedly more males females have, and die from, peptic ulcer. This may be due to a sex none, to the higher average gastric acidity of the male, to the social onsibilities placed on the male, or to the presence in females of more growth and repair promoting factor. A combination of these factors be involved.

We interpret the evidence as indicating that gastric and duodenal r are manifestations of the same disease entity, that certain exogenous ogic factors determine whether a duodenal or gastric ulcer occurs, and the secretion of acid is more involved in the genesis of duodenal than ic ulcer.

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OUTLINE OF CHAPTER 18

Psychosomatic Etiology of Peptic Ulcer

I. Introduction
  A. the question of wartime increase in peptic ulcer
    1. Comment
II. Psychosomatic Theory
III. Personality Characteristics of Peptic Ulcer Patient
  A. chronic fear (draper et al.)
  B. repressed oral-receptive tendencies (alexander)
  C. anxiety, insecurity, resentment, guilt, and frustration (mittelmann and wolff)
  D. comment
IV. Effects of Emotion on Gastric Secretion and Motilit
  A. effects of emotional stress in animals
  B. effects of emotional stress in man
    1. Effect of Emotional Stress on Gastric Secretion
    2. Effect of Emotional Stress on Motility
    3. Comment
V. Relation of Hypermotility and Hypersecretion Peptic Ulcer
  A. hypersecretion and peptic ulcer in experiment animals
  B. hypersecretion and peptic ulcer in humans
VI. Discussion
VII. A Suggestion Regarding Terminology
VIII. Summary

HAPTER 18

Psychosomatic Etiology of Peptic Ulcer

Introduction

In previous chapters, reference has been made to the effect of changes environment on the occurrence of peptic ulcer and on the death rate d incidence of the complications of peptic ulcer. Observations have been esented indicating the effect of war, heavy air raids, marital state, cial class, population density, and social customs on the death rate and e incidence of the complications of peptic ulcer. Studies have been cited here conflicts due to various causes have apparently been the exciting use of the onset of peptic ulcer. Some evidence has been cited indicating at peptic ulcer tends to occur in a person with a driving, conscientious, bitious type of personality.

These facts are known to every student of the problem of peptic ulcer. eryone who has had even a small experience in the management of ptic ulcer patients must be convinced, as we are, that tension-producing nflicts or psychic traumata are exciting causes of recurrences in many tients.

It is important to decide whether psychic factors operate to cause the sease or merely to aggravate it. It is recognized that physical and mental t is important in determining the course of tuberculosis but myco-cterium tuberculosis is the primary etiologic agent. In considering the tient as a whole, proper but not undue emphasis should be placed on e psychic aspects of the disease.

One could make a long list of diseases which are alleged to be excited caused by mental conflicts and trauma and which are improved by the moval of the conflict, such as ulcerative colitis, spastic and mucous litis, angina pectoris, hyperthyroidism, and hypertension. Yet we nnot conclude that the mental conflict was the prime cause of the sease.

Why do the same type of conflicts in one patient appear to excite ptic ulcer, in another angina pectoris, in another colonic disturbances, another hypertension, in another skin disease, and in another bronchial thma? Does this mean that the cerebral area concerned with emotion one case stimulates that part of the hypothalamus which innervates the

lesser curvature of the stomach, in another patient the prepyloric region, in another the duodenal bulb, in another the colon, in another the coronary arteries, in another the peripheral arteries, in another the skin, etc.? Or does it mean that the emotional state, through the hypothalamus, simply excites a latent disturbance whether it be in the stomach, duodenum, colon, heart, thyroid, skin, or blood vessels? These are difficult questions to answer with completely acceptable evidence at present.

Moreover, it appears that factors other than psychic ones serve as exciting causes for the recurrence of ulcer, as is true of hypertension, hyperthyroidism, angina pectoris, asthma, and certain other diseases. We are just as certain that in some ulcer patients upper respiratory infections, dietary indiscretions, irregular sleeping and eating, bolting of rough food, and excessive smoking and drinking are exciting causes for recurrences as we are certain that psychic conflicts are. But we cannot prove our contention nor state in all cases how the exciting causes work. We can demonstrate in animals, however, that rough food and respiratory infections are chronicity factors.

The Question of Wartime Increase in Peptic Ulcer

According to the record, war does not appear to have a uniform effect on the incidence of ulcer. In World War I, neurocirculatory asthenia or effort syndrome received much attention. Hurst, a gastroenterologist, in his book on the medical diseases of the war (World War I) has no discussion on dyspepsia. The Germans noted an increase in dyspepsia; some attributed it to gastric ulcer and others to gastritis incident to the poor diet high in roughage. Little evidence of real peptic ulcer was submitted. In the U. S. Army, the rate of gastric ulcer was 0.42 per 1000 and duodenal ulcer, 0.26 per 1000. Kantor, in the report of his experiences during World War I, diagnosed 24 cases of duodenal ulcer, four cases of gastric ulcer, and 113 cases of gastrointestinal neurosis out of 311 gastrointestinal patients (1).

On the contrary, in World War II peptic ulcer received a great deal of attention, particularly in the early phase of the war. Dyspepsia at one time accounted for as high as 15 to 20 per cent of the medical conditions in the British Army and peptic ulcer was diagnosed in 52 per cent of the cases of dyspepsia (2). Friedman (3) has reviewed a collected series of 13,000 cases of dyspepsia from the recent "war literature" and found that peptic ulcer accounted for half of the cases and functional disturbances for most of the remainder. The incidence of peptic ulcer in the Army of the United States was approximately 3.0 per 1000 (0.30 per cent) or four times the incidence in World War I. For overseas troops, the rate ranged

from 1.4 to 2.3 per 1000 and for those in the United States from 2.9 to 4.2 per 1000 (3).

As pointed out on p. 492, it was uncertain what proportion of the ulcer patients in the British, Canadian, and U.S. Army represented an increase in new cases. The estimates in the literature (3) range from 10 to 55 per cent, the average being approximately 25 per cent. The only figure for the rate at which new cases form in a male population is 0.30 per cent per year derived from the observations of Jennison cited on p. 606. This is the rate of peptic ulcer in the U.S. Army as a whole and hence it cannot be stated that the rate of increase was greater in the Army than in the civilian population. Thus, the increase between World War I and World War II is most probably due to an increased recognition of the disease and to an actual increase in the general incidence of peptic ulcer in males which occurred between the two wars. The increase started about 1912–1915 and continued to about 1935 (Table 86, p. 610).

The mortality statistics also show a difference in the incidence of ulcer during the two World Wars. In World War I, as shown in Fig. 100, p. 609, the death rate from peptic ulcer declined in the United States, England, and Denmark and leveled off in Sweden. During World War II, it remained the same in the United States (Table 86, p. 610) but increased during the heavy air raids in England and at the height of the war strain in England, Sweden, and Norway. The same is true for perforations and hemorrhages, but there is no good evidence to show an increased incidence of peptic ulcer during the same period in England and Sweden. However, acceptable evidence from Switzerland shows an increase in the incidence of peptic ulcer involving an increase in the number of new cases as well as recurrences in the old (4, 5). The Swiss were also exposed at the same time to a low protein diet containing much vegetable roughage. It is interesting to note that after World War I controversial discussion occurred in Germany, where a low protein, high roughage diet prevailed during World War I, regarding whether the incidence of new cases of peptic ulcer was increased. This controversial point was not settled because of lack of adequate evidence.

Those who have collected and presented the data on the effect of air raids have expressed the opinion that anxiety, fear, and the loss of relatives by death were the contributory causes. Kretchmar (4) in Switzerland has reported an increase in the incidence of recurrences of peptic ulcer and its complications in Switzerland for both World War I and World War II. He believes that the cause of the increase in both wars was the high vegetable-cellulose or rough diet the population had to consume. The increased consumption of vegetables occurred in all European countries

during both wars. Markoff (5), who also reported on the increase incidence of peptic ulcer in Switzerland in 1941-1942, ascribed t increase to undue strain on the nervous system provoked by the w Kretchmar (4) provides a table showing that almost all of the alimenta tract diseases, including appendicitis and gastric cancer as well as hern increased in rate in the Swiss Army after mobilization.

Much study was directed toward ascertaining the personality patte of the soldier and sailor with peptic ulcer during the war. The int pretations of the results of such studies vary widely. A summary is p sented in Table 111. It is clear from this evidence that neurotic traits a

Table 111

FREQUENCY OF NEUROTIC TRAITS AND N.P. DIAGNOSES IN PATIENTS WITH PEPTIC ULCER AND FUNCTIONAL DYSPEPSIA*

Author	*Peptic Ulcer*					*Functional Dyspepsia*				
	Total No. Cases	*Neurotic Traits*		*N.P. Diagnosis*		*Total No. Cases*	*Neurotic Traits*		*N.P. Diagnosis*	
		No. With	*Per Cent With*	*No. With*	*Per Cent With*		*No. With*	*Per Cent With*	*No. With*	*Per Cent With*
Friedman (3)	46	6	13	2	5	92	58	62	30	33
Montgomery, Schindler, et al. (11)	23	4	18	0	0	22	6	27	11	50
Halsted & Weinberg (6)	200	40	20	10	5	110	12	9	93	84
Total	269	50	18	12	6	224	76	34	134	60

* Kirk (7) and Schildkrout (13).

psychoneurosis are more commonly encountered in patients with f tional dyspepsia than in patients with peptic ulcer. Halsted and Wein (6) state that the symptoms of the ulcer patient, in contrast to those o patient with "psychogenic dyspepsia," had no direct connection wit feeling of anxiety or insecurity. Kirk (7) finds that the soldier with p ulcer is no different emotionally from any other soldier. Apparently life did not cause peptic ulcer to appear or to recur in a person w certain well defined personality pattern or characteristic emotional

Unfortunately, we cannot ascribe the decisive increase in perfora (p. 551) and hemorrhages in London during the heavy air rai anxiety, fear, or insecurity or to psychic trauma alone. Under such tions, a multiplicity of environmental factors may operate in ad

ychic trauma, such as irregular sleep, irregular eating, changes in
a poor diet, excessive smoking and drinking, oral sepsis, increased
ure, and the catching of colds. But it cannot be stated that any of
additional factors have been clearly demonstrated to be contributory
rs. Irregular modes of living, sleeping, and eating have not been
nstrated to be a decisive factor. Bashford (8) in 1935 compared the
nce of ulcer in postal employees whose duties did and did not
re an irregular mode of living. There were 70,000 employees with
ular and 12,000 with regular duties. In the two groups the ratio of
ces due to peptic ulcer was 7:6, which indicates that an irregular
of living is not decisively contributory. Little is known regarding
ffect of changes in diet and roughage in the diet on gastric secretion
idity. Curschmann (9) and Grote (10) report that a change to a diet
aining much cellulose, such as cabbage and carrots, increases gastric
ty. (This work calls for repetition with better methods.) Clinically,
sive smoking is believed to be almost as strong an excitatory cause
ptic ulcer as anxiety or frustration. This belief has some well designed
riments and some statistically significant evidence in its support
894), but further studies are needed. The ingestion of alcoholic
rages and excessive use of caffeinated beverages is believed to be an
atory cause. The academic evidence, and some of the clinical, we
ve, supports such a view. Further evidence is required before it can be
luded that oral sepsis and upper respiratory infections are decisive
atory causes.

COMMENT. It is our opinion that no single so-called excitatory factor
been unequivocally demonstrated to cause the onset or recurrence of
ic ulcer.

Although not proven, it is our opinion, based on the evidence available,
anxiety or psychic trauma is an excitatory cause of peptic ulcer in
ons predisposed to ulcer. We also believe that the observations showing
ncrease in perforations and hemorrhages from peptic ulcer in England
ng the period of heavy air raids unequivocally established the fact
environmental changes may excite recurrences. It seems certain to
at anxiety and the other unhygienic aspects of living which frequently
mpany anxiety served as an excitatory cause. Yet we do not believe
anxiety or a conflict is the sole excitatory cause of peptic ulcer.

The observations made in England during the war, the observations
e by Beaumont and others since him that emotional states affect
ic secretion and motility, and the observation of many discerning
icians that recurrences of peptic ulcer frequently coincide with or
w periods of emotional stress commands that research be directed to
rmine whether psychic factors cause or excite peptic ulcer in ulcer-

susceptible or nonsusceptible persons and, if so, to ascertain the mecha-nisms concerned.

Psychosomatic Theory

In 1913, Bergmann (14) proposed the theory that peptic ulcer is caused by an imbalance of the autonomic nervous system. The effects of this imbalance are manifested in the stomach by spasm, ischemia, damage to the mucous membrane, and peptic digestion of the devitalized area. The resulting acute lesion initiates further spasm, thus establishing a vicious cycle which leads to a chronic ulcer. According to Bergmann and his disciples, the "spasmogenic" ulcer arising from a "vegetative disharmony" occurred in individuals of a "neurotic" disposition. Hence they introduced the term "neurotic duodenal ulcer" (15).

While Bergmann (16) described the "vegetative imbalance" as involving the entire autonomic system rather than one of its divisions, Cushing (17) proposed in unmistakable terms that the primary disturbance in many cases of peptic ulcer lies in the parasympathetic component (see Chap. 12). He envisioned the mechanism as follows: from a parasympathetic center in the diencephalon, fiber tracts pass to autonomic stations in the midbrain and medulla. Experimental lesions anywhere in the intracranial course of these fiber tracts from anterior hypothalamus to vagal center are prone to cause gastric erosions or acute ulcers. Cushing (17) postulated two possible sources of disturbance which could initiate excessive discharge over the parasympathetic pathways: (1) a diffusion of the secretion of the posterior pituitary into the hypothalamic region and/or into the cavity of the third ventricle, and (2) cortical or psychic influences. "So it may be," Cushing wrote (17), "that highly strung persons who incline to the form of nervous instability classed as parasympathetic (vagotonic), through emotion or repressed emotion are particularly prone to have chronic digestive disturbances with hyperacidity often leading to ulcer." This concept sets forth the three major premises upon which the present day psychosomatic theory of the etiology of peptic ulcer is based, viz.: (a) that most ulcer patients manifest a characteristic personality pattern or conflict-situation; (b) that this emotional status is accompanied by hypersecretion and hypermotility of the stomach or some other change in the secretions or vascularity of the stomach and duodenum; and (c) that hyperactivity of the stomach or some other functional alteration leads to peptic ulcer.

We shall now examine the premises upon which the psychosomatic theory was evolved and review the experimental evidence which has been advanced to support it.

Personality Characteristics of Peptic Ulcer Patients

Alexander (18) points out that the studies by internists and physiolo-sts fall short of an accurate evaluation of the deeper psychologic forces otaining in a given patient. This is, however, to be expected, since such udies require special training and experience. Furthermore, according Alexander, not even a careful psychiatric anamnesis can be fully bstituted for the analytic approach in uncovering the psychic factors ausative of a somatic disturbance. It would appear, then, that in the terests of greatest accuracy a review of the evidence for a common enominator of the emotional status of peptic ulcer patients should be ncerned only with the work of specialists. This simplifies the problem aterially, because it narrows our survey to three basic contributions.

Chronic Fear (Draper, et al.)

Considerable difficulty is encountered in following Draper's argument the psychic pattern in peptic ulcer. In 1927, Draper and McGraw (19) otained evidence that in the psychologic, as in the morphologic, panel ulcer patients, maleness was the essential feature. Male members of the lcer race" were described as having a strong heterosexual urge, whereas e masculine component in the female ulcer patient was described as a diminished interest in erotic experience." These observations were nsidered to be consistent with the fact that the incidence of peptic ulcer much higher in males; i.e., it is a male disease, or a disease of maleness.

In 1932, Draper and Touraine (20), influenced by Crile's report on e relation of hyperthyroidism and peptic ulcer, were compelled to consider the validity of their "male disease" thesis. Crile (21) had inted out that: (a) the vegetative disturbance in exophthalmic goiter is milar to that in peptic ulcer patients; (b) hyperthyroidism was associated ith hyperactivity of the stomach; and (c) five cases of peptic ulcer were pparently cured by partial thyroidectomy and left adrenalectomy. raper and Touraine continued:

> In addition to these observations of Crile, it is commonly known that exophthalmic iter and hyperthyroidism are from six to eight times more frequent in women than in en. . . . In view of these considerations, consequently, it would appear paradoxical at more men than women should be affected with ulcer. The only explanation for is paradox seemed to be in the fact of femaleness within the male.

Accordingly, the authors re-examined the literature and their own ase histories and observations, and on deeper psychologic investigation ey were able to identify a "masculine protest." "A man who possesses

that degree of femaleness which threatens the authenticity of his essenti maleness becomes subjected to deep-rooted, unconscious fears lest he fa in his attempt to play successfully the masculine role in life."

It is inconceivable that Draper and Touraine's concept of "femal ness within the male" to describe the psychic conflict in peptic ulc patients was actually arrived at by the approach indicated in their pape What we do not understand is: (a) why the authors felt impelled t reorient their studies on the basis of unconfirmed and physiologicall inadequate data—as a matter of fact, in Crile's report *there was no data all;* and (b) why the authors resorted to a patent *non sequitur* as a justific tion for reinterpreting the ulcer patient's gynandropsychic status.

At any rate, in the most recent publication on this subject by Drap and his associates (22), it appears that "femaleness" or the "femini component" is no longer considered to be the main feature, although it still a factor. "Especially does it seem that unconscious awareness of t feminine component may be a stimulus to the overexploitation of th virility which is so characteristic of ulcer bearers." The essential poi in the psychic panel was "the fear emotion arising from various stim lating mechanisms." The sources of this fear are presented in Table 11 taken from Draper et al.

Table 112

DISTRIBUTION OF CHIEF FEAR SOURCES AS ELICITED IN THE GROUP OF 80 CASES*

	Present		*Absent*	
	No.	*Per Cent*	*No.*	*Per C*
1. Inner sense of insecurity based on actual or supposed physical inferiority, including gynic emphasis	63	84.0	12	16
2. Persistent hold on mother principle and fear of loss of mother surrogate's approval	76	97.4	2	2
3. Jealousy and aggression	50	64.9	27	35
4. Guilt and fear related to sex problems	31	49.2	32	50
5. Compensatory striving	41	56.2	32	43

* From Draper et al. (22).

Out of 80 cases a few failed to supply adequate information in one or another of five categories. Hence the total number of cases varies in each.

Concerning the "persistent hold on mother principle and fear of of mother surrogate's approval," which appears to be the most consis source of fear in the group studied, Draper et al. write:

When you read the intimate histories of persons who have ulcers . . . the im sion develops that these individuals, like frightened neglected children, are str

ually to recapture and maintain the mother principle which had ministered so ulously to the demands of that delicate infant receptacle for milk.

he next paragraph begins, "The more one observes these victims of nic fear . . . ." Thus, "fear," "fright," and "frightened" are the ls recurring throughout Draper's discussions of the psychic status of ic ulcer patients, so we must presume that he considers chronic fear the dominant emotional force in these patients.

Repressed Oral-receptive Tendencies (Alexander)

tudies undertaken at the Chicago Institute for Psychoanalysis under direction of Alexander (18) have resulted in the formulation of a owly definitive hypothesis regarding the basic psychologic personality lem in peptic ulcer patients. The program was guided by three as-tions: (a) that the psychic factors causative of the somatic disturbance of a specific nature; (b) that conscious psychologic processes play a rdinate role in the causation of somatic symptoms, since such con-s emotions and tendencies can be freely expressed and relieved ugh the voluntary system; (c) that the patient's actual life situation lly has only a precipitating influence on the disturbance.

he author thus assumed, *a priori*, that there was to be sought in these nts not a distinctive personality pattern, but rather a typical conflict-tion, and the aim of his studies was to identify this conflict. The second mption is a gratuitous one; certainly conscious emotions can be ex-sed through the voluntary nervous system, but clinical observation has n repeatedly that in many peptic ulcer patients the outward appear-of self control is carefully maintained. The third assumption, namely, the environmental circumstances are not the basic cause but only the ipitating factor, corresponds with the general clinical impression.

On the basis of psychoanalytic treatment of six cases of duodenal ulcer three of gastric neuroses, it was determined that "in most cases the al conflict-situation can be described as the rejection of strong oral-ptive tendencies on account of their incompatibility with the aspiration e ego for independence and activity."

Alexander states that, although certain personality types might be e likely to become involved in this conflict-situation, he has observed in appropriate circumstances other types of character may develop the conflict. He cites the case of a man who, unlike the usual ulcer pa-, had little ambition, drive, or urge to excel. During many years of riage with a woman who thwarted his receptive tendencies, he de-ped gastric symptoms and eventually a peptic ulcer. After a severe orrhage from the ulcer, he established relations with another woman motherly type, and all his symptoms disappeared.

"This one example alone," Alexander writes, "shows that it is thwarting of receptive cravings and not a certain personality type that primary importance." With this statement we cannot agree be neither the cited case nor any other one single case could possibly p that: (a) the thwarting of receptive cravings is generally of primary tance in the genesis of gastric symptoms or (b) that the personality ty generally not a factor. Moreover, while the nine cases (six duodenal u three gastric neuroses) reported by the Chicago group certainly repres considerable amount of time and effort, they cannot in our opinion b cepted as establishing the concept of repressed oral-receptive tendenc the basic conflict-situation in peptic ulcer.

Anxiety, Insecurity, Resentment, Guilt, and Frustration (Mittelmann and Wolff)

The personality features and reactions of 50 patients with peptic or gastric neurosis were studied by Mittelmann and Wolff (23). found a wide range of personality types which, however, shared a co and characteristic reaction pattern which consisted of intense anxiet security, resentment, guilt, and frustration. Thirteen "normal" su were studied as controls, but oddly enough the personality findings controls were not disclosed. In the protocols, brief personality sketc two "normals" included the following characterizations:

Subject 1: . . . dissatisfied with his work, waking of times at night, concerned whether he had "attended to everything" at his work . . . admired his el resented the fact that the latter criticized his co-workers . . . sexual relati which were unsatisfactory because of premature ejaculation . . . was ob worried about it . . . under anxiety about his work he had sinking sensations stomach . . . during continued disappointment he lost his appetite.

Subject 3: In his early childhood he had been "nervous" and was particularly of the dark and of storms . . . unusually anxious about examinations . . . ever a new examination or treatment was anticipated, he felt anxious and i . . . masturbated occasionally but not without feelings of guilt.

It would appear that emotions of anxiety, resentment, guilt, an were present in the controls, at least in the only two whom the a described. Of course, it is possible that the difference between the co and the ulcer group was one of intensity; to what extent this obtai the material under study cannot be determined from the report be while the life histories and personalities of the ulcer patients were d at considerable length, little space was devoted to the controls.

Comment

It is interesting to note that psychiatrists, for example, Alexand Wolff, find that peptic ulcer patients and patients with functiona

("gastric neuroses") manifest the same type of personality structure
flict situation, whereas gastroenterologists (3, 7, 11) stress the sharp
nce in the makeup of these two classes of patients.
e objective assessment and categorization of personality and emotion
viously difficult, and the discrepancies which have been pointed out
intended to minimize the importance of these studies. However, the
at it is difficult to accomplish does not permit us to be satisfied with
an scientifically adequate data. Specifically, the need for control
a fundamental of scientific method, must be met. These are the con-
tions which motivate this critical analysis.
e anticipate that the apparent inconsistencies will be resolved by fu-
vestigation. At present, the fact remains that the first premise upon
the psychosomatic theory of peptic ulcer is based has not been
established.

Effect of Emotion on Gastric Secretion and Motility

e most obvious potential etiologic feature of the pathologic physi-
of peptic ulcer is hyperactivity of the stomach as regards both its
and secretory functions (24). One of the premises of the psycho-
c theory is that this hyperactivity can and does accompany emo-
states or conflict-situations. Alexander (18) envisions the relationship
ows:

e intense wish to receive, to be loved, to depend upon others, is rejected by the
go and consequently cannot find gratification in normal life relations, then only
ressive pathway remains open; the wish to be loved becomes converted into the
be fed. The repressed longing to receive love and help mobilizes the innervations
stomach which are since the beginning of extra-uterine life closely associated
e most primordial form of receiving something, namely with the process of
g food. These innervations serve as a chronic stimulus of the stomach functions
d to its dysfunction since this stimulus of the stomach is independent of the
organically conditioned stimulus, namely the need of food; this stimulus has
n in emotional conflicts entirely independent of the physiologic state of hunger.
ndividuals who on account of the described conflict-situation have to repress
negate their over-strong receptive cravings express them in the tacit physiological
e of the stomach functions. Such a stomach behaves all the time as if it were
or were about to take in food.

tuelmann and Wolff (23) consider that an excessive secretion of the
h under stress may be a manifestation of an attempt to resolve hos-
nd gain security through eating. The hypersecretion might, they
, represent preparation for eating the prey or enemy.
ese hypotheses represent an important development in our concept
effect of emotions on digestive functions. They imply that certain
surable or dysphoric affective states cause an *augmentation* of gastric

activity—a change hitherto considered to be associated only with pleasurable feelings. We must, therefore, inquire to what extent this postulation of these psychologic mechanisms is justified by physiologic evidence bearing on the relationship between emotions and gastric activity. More specifically, it is necessary to determine whether or to what extent the stomach differs in its response to emotions of different types. Observations have been reported on changes in gastric secretion or motility, or both, under conditions of emotional stress in animals and man.

Effects of Emotional Stress in Animals

The extensive literature on this point will not be detailed here. Suffice it to say that in every report available to us, it has been concluded that the only effect of dysphoric emotional states on the gastric function in animals is *inhibition*. Whether the emotion was one of fear, anger, or frustration, the effects have been the same, namely, a decrease in glandular and muscular activity of the stomach. However, it may be argued that one could hardly distinguish with any reliability what kind of emotion an animal was experiencing.

Effects of Emotional Stress in Man

In reviewing the reports prior to those of Mittelmann and Wolff (23) and Wolf and Wolff (25), we will consider the effects on secretion and motility separately, because the earlier studies did not investigate both simultaneously.

Effect of Emotional Stress on Gastric Secretion. Beaumont (26) observed that fear and anger were among the factors associated with inhibition of gastric secretion. Hornborg (27), Bogen (28), and Schrottenbach (29) reported dimunition in gastric secretion as a result of anger or vexation. Each of the latter authors performed their experiments on fistula cases, and in each instance the subject was a child less than six years of age. Moreover, the emotional stress produced was not very strong or of long duration; it amounted to what we would describe as teasing; i.e., the child was shown food but was not permitted to eat it, or was deprived of a toy, or was made to cry by a pinch of the arm.

Mantelli (30) stated that immediately after a "severe psychic disturbance" and lasting up to three hours, there is a marked inhibition of gastric secretion. No data were presented and the nature of the psychic upheaval was not disclosed. Heyer (31) purported to show that a brief period (five minutes) of emotion, euphoric or dysphoric, produced in hypnotized volunteers by suggestion (war experience, choking, winning a lottery, railroad accident, etc.) resulted in a reduction of the secretory response to suggested food. The data given to illustrate the effects were chosen arbitrarily from

all of the experiments; the total number of experiments is not mentioned, however, so there is no way of knowing whether the observed changes occurred in five out of 10 experiments, or five out of 30. It may be questioned whether a "suggested" meal provides a consistently dependable secretory test. For example, Heyer states:

> Although the aspirations after a real test-breakfast still yield the previous normal values, the oft-repeated and in a true sense really deceptive suggestions appear no longer to have the proper effect on the amount of flow and also on the HCl-concentration. We had to let go a great number of experimental subjects because the volume of juice and the free acid decreased progressively.

If this be so, then one must be extremely circumspect indeed in interpreting data on the effects of "suggested" emotions on "suggested" meals.

Wittkower (32) studied the effect of suggested emotion, partly under hypnosis and partly in the waking state, on the secretory response to a caffeine test-drink. His results were summarized as follows: (a) similar affects in a given subject cause similar changes; (b) similar emotions cause various changes in different subjects; and (c) various emotions cause similar changes in the same subject. Moreover, there are certain individuals who react with an increased acidity regardless of the emotional state; there are others who show decreased acidity regardless of the affective state; and in other subjects the changes are manifest in the volume, without alteration of the acidity.

We find Wittkower's work extremely difficult to evaluate. His "normal" curves are said to represent the consistent response to the test-meal over a period of several days. Assuming that the "normal" curves shown represent the averages, then the spread must have been considerable, judging from the peculiar shape of some of these curves. And, in evaluating the response to suggestions given to hypnotized patients, one must keep in mind that the hypnotic state itself may be accompanied by a rise in acidity, as shown by Luckhardt and Johnston (33).

One of Wittkower's (34) conclusions taxes one's credulity and the work requires confirmation before it can be given credence. He claims that in a great majority of cases (eight out of 12 subjects), a feeling of intense disgust was associated with *increased* secretion. "We conclude from our investigations that intense aversion for food, just as a desire for food, evokes abundant secretion and acidity in the gastric juice and that appetite is for the most part independent of gastric juice and acid formation." This is a unique and important observation, if true.

In 1920 there were reported two observations of significance, although the paucity of the data discourages any generalizations. Miller, Bergeim, and Hawk (35) determined the gastric secretory curve in response to a

test-meal on a freshman medical student (a) while he was in a state of anxiety over the outcome of an examination, and (b) a week later, "under the best mental conditions." Comparison of the two curves reveals that during the anxiety period gastric emptying was delayed and the acidity markedly elevated. Bennett and Venables (36) showed curves of a similar pattern in an experiment on an ex-World War aviator who had had "sufficient association with extreme danger to know the meaning of the word anxiety." Under light hypnosis, the subject was told that he was flying in foggy weather and was forced to attempt a landing in hostile territory. There was a preliminary sharp rise in acidity, then inhibition, then a secondary rise; gastric emptying time was prolonged to almost twice the control value.

It is not known, in either of the above instances, whether the retention of food in the stomach was due to a loss of tone, i.e. an inhibitory effect of the emotion, or whether it was due to pyloric or antral spasm, i.e. an augmentory effect. The distinction is important because it involves the question of whether the secretory increase was a concomitant effect or was secondary to the retention of the test-meal. No such uncertainty, however, enters into an observation reported recently by Hoelzel (37). Hoelzel had made daily observations for many years on the acidity of his fasting gastric contents, and it was therefore well established that his fasting acidity ranged from 0.0 to 0.13 per cent. On the morning after his landlady was shot, his fasting acidity was 0.26 per cent. It remained above 0.17 per cent for the ensuing 10 days, during which he feared he might be a victim of revenge because he had been responsible for the arrest of the culprits involved in the shooting. After he moved to a location where he felt entirely safe, the free acid fell to its customary level. Perhaps the most interesting aspect of this case is Hoelzel's statement, "It was only after finding my gastric acidity doubled that I would have been willing to admit that I was definitely upset and feared being shot."

Gordon and Chernya (38) reported observations which, had they been supported by data, would be of paramount importance. They had the unusual opportunity of studying four gastric fistula patients, in two of whom the surgical methods used for plastic reconstruction of the esophagus created a temporary esophagoenterostomy. Ten graphs are presented showing the effects on gastric secretion of feeding various test meals, of sham-feeding, of tempting the patient with appetizing food, of hypnotic suggestion, and of alterations in the blood sugar level. But when it comes to the effect of sustained emotion, there is no data whatever, only this statement:

> One of our patients, who gave regular and consistent curves of secretion, toward the end of his stay in the clinic became nervous and homesick and resentful of

xperiments. His type of secretion changed definitely; both on fasting and after introuction of a stimulus he began to give a very high secretion. His secretion lost its hasic character and became continuous.

Effect of Emotional Stress on Motility. In one of his observations, Beaumont (26) ascribed a delay in gastric emptying to the fact that St. Martin was in a state of violent anger. Carlson (39) stated that "actual nxiety causes temporary inhibition" of the hunger period. In one inance, Carlson writes:

When preparing to introduce 200 cc. of 0.5 per cent acetic acid into the stomach in ne midst of the period of powerful hunger contractions, Mr. V. somehow thought that ve intended to introduce that much concentrated acid (or vinegar). As we were going bout with the preparations it was noticed that the stomach contractions suddenly ecame very feeble. Mr. V. looked worried. We inquired if he did not feel right, and e asked if we intended to put all that vinegar into the stomach. "It will surely hurt ne," he said. To assure him, the author drank half of the acid himself, and then asked im to take a mouthful of it. Then he laughed and said, "Oh, I thought it was pure inegar." In two minutes after the mental stress and anxiety were over the hunger ontractions returned to their normal rate and amplitude.

The extensive work of Brunswick (40) is of little value for the present roblem, inasmuch as (a) the purpose of his investigation was not rimarily to determine what changes take place in the stomach in conection with affective states, but rather to test the Lange theory that motions are the perceptions of bodily changes; and (b) the methods used o produce the emotional disturbances were more in the nature of "stunts," .g. turning off the lights, shooting a pistol, dashing water in the subject's ace, holding a wriggling snake in front of the subject, electric shocks, etc. No observations were made on the effects of sustained emotional tension.

The painstaking investigations of Todd (41) on the physiology of the uman stomach stand as the turning point in our conception of the effects f emotion on gastric motility. Extensive radiographic observations on nedical students enabled Todd to discern characteristic motility patterns or various affective states. He showed that sudden or transient dysphorias uch as mental shock, acute disappointment, fear, or depressing mental train were accompanied by decrease in gastric tonus and weak or absent eristalsis. On the other hand, he found that in the "anxiety complex" he stomach always manifested hyperactivity. He states:

Since there is no distinction in pattern between it and the hyperactivity which recedes pyloric or duodenal ulcer, precautions should be taken to determine its ransient or quasi-permanent form. If the hyperactivity is still present some general dvice is distinctly indicated.

On the basis of three mucosal relief studies, Wittkower (32) concluded hat in affective states there can occur a change in the mucosal pattern

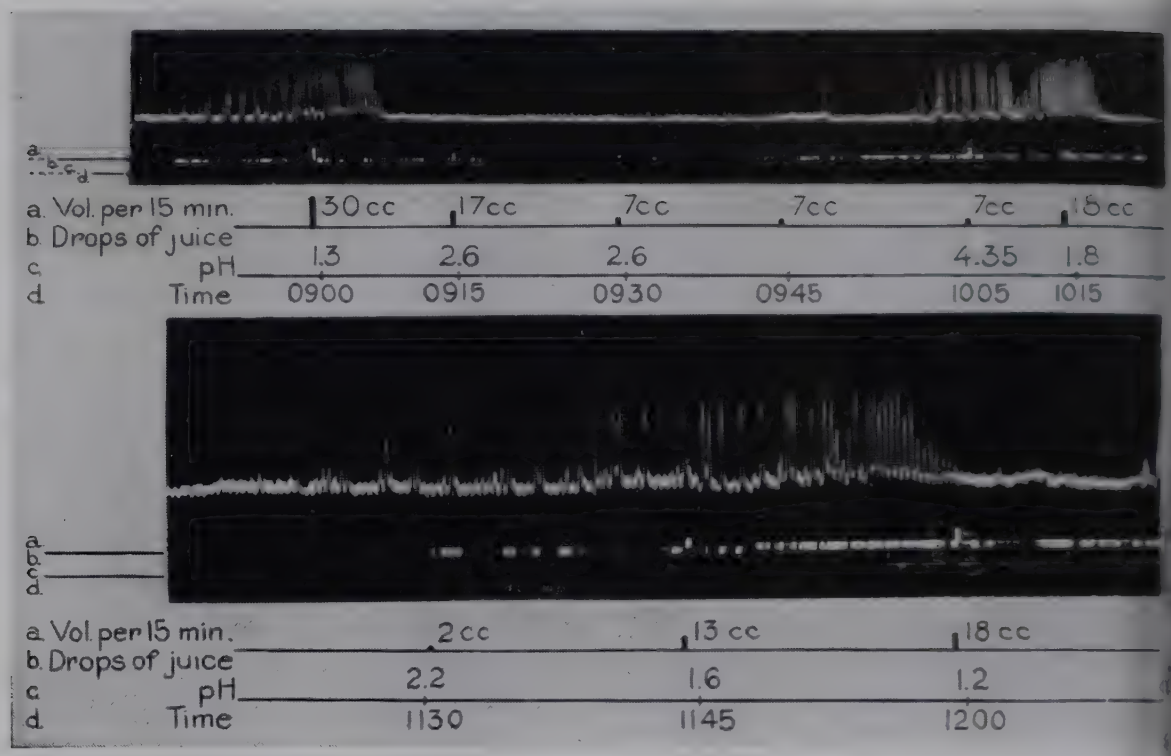


FIG. 106. A control observation of 3½ hrs. duration. Three "hunger motilit periods of generally similar configuration and duration occurred. Secreto activity accompanied the motility periods. Increased activity generally parallel the increased volume.

("without demonstrable direct participation of the muscularis prop mucosae") similar to that hitherto interpreted as gastritis. Charmandarj et al. (42) published a preliminary note on some of their observatic regarding changes in the digestive tract accompanying various affe induced by hypnotic suggestion. Generally, pleasurable emotion rai the tonus while sorrow inhibited it. In other dysphoric states, " stomach reacted more stormily" the more vividly the individual perienced the emotion. The authors did not consider any generalizati justified on the basis of the work reported.

Barron and his associates (43) reported an increase in the amplit of stomach contractions as measured kymographically in patients al to undergo surgery. They did not, however, regard their evidence sufficient to permit conclusions concerning the type of emotion invo or the uniformity of the response.

In 1938, McGregor (44) stated, "Enough evidence has now b produced to show that gastric peristalsis and secretion are arrested in not only by worry, anxiety, fright, fear and the major affective st but also by much finer shades of feeling." However, from the repor we have summarized them, we would conclude that prior to 1938 t was suggestive evidence that gastric secretion may be increased, and evidence (Todd et al.) that motility may be augmented, in emot

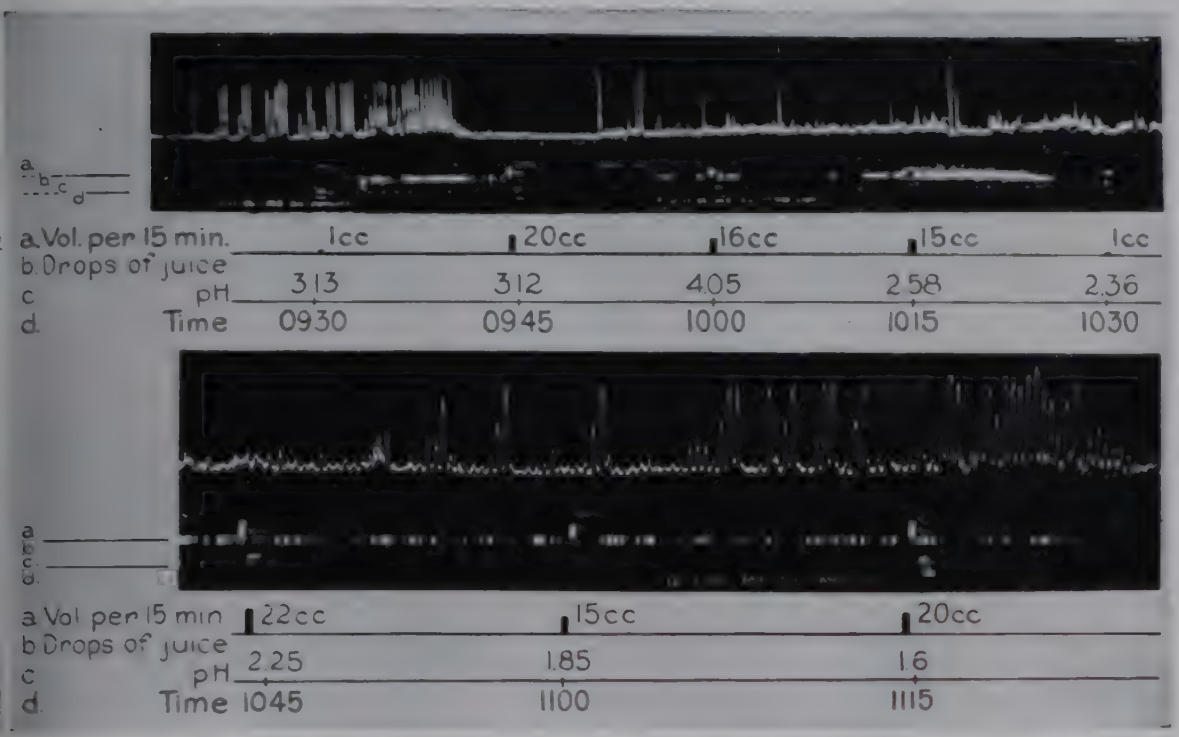


FIG. 107. After a hunger motility period similar to those observed in previous control records, an interview is begun in an attempt to induce anxiety, resentment, and frustration. There is no apparent stimulation of motility; on the contrary, there is a question whether a spontaneous period of motility and secretion might not have supervened had not emotionally charged material been discussed. Within a few minutes after discontinuing the interview, secretion and motility appeared, with gradually increasing acidity.

states. The recent work of Mittelmann and Wolff (23) and Wolf and Wolff (25) appears to demonstrate conclusively for the first time a simultaneous augmentation of acid-pepsin secretion and motor activity of the stomach accompanying certain affective reactions.

The importance of this work should stimulate early confirmation. We feel that repetition of the investigation is required. It has been our experience that at least five hours of study a day for several days with a balloon in the empty stomach is required to obtain a fair idea of the motility pattern of the stomach of a normal subject or an ulcer patient. In work of this type, sufficient control and test data should be available to demonstrate a statistically significant difference between the average of the control and test data.

To illustrate the problems of interpreting data from gastric function studies, we reproduce here some tracings obtained on a patient with duodenal ulcer (Figs. 106, 107, and 108).* These are not "typical" of the findings in ulcer patients generally, because we have not been able to

*These tracings were made available for publication through the courtesy of Dr. H. M. Pollard, University Hospital, Ann Arbor, Michigan.

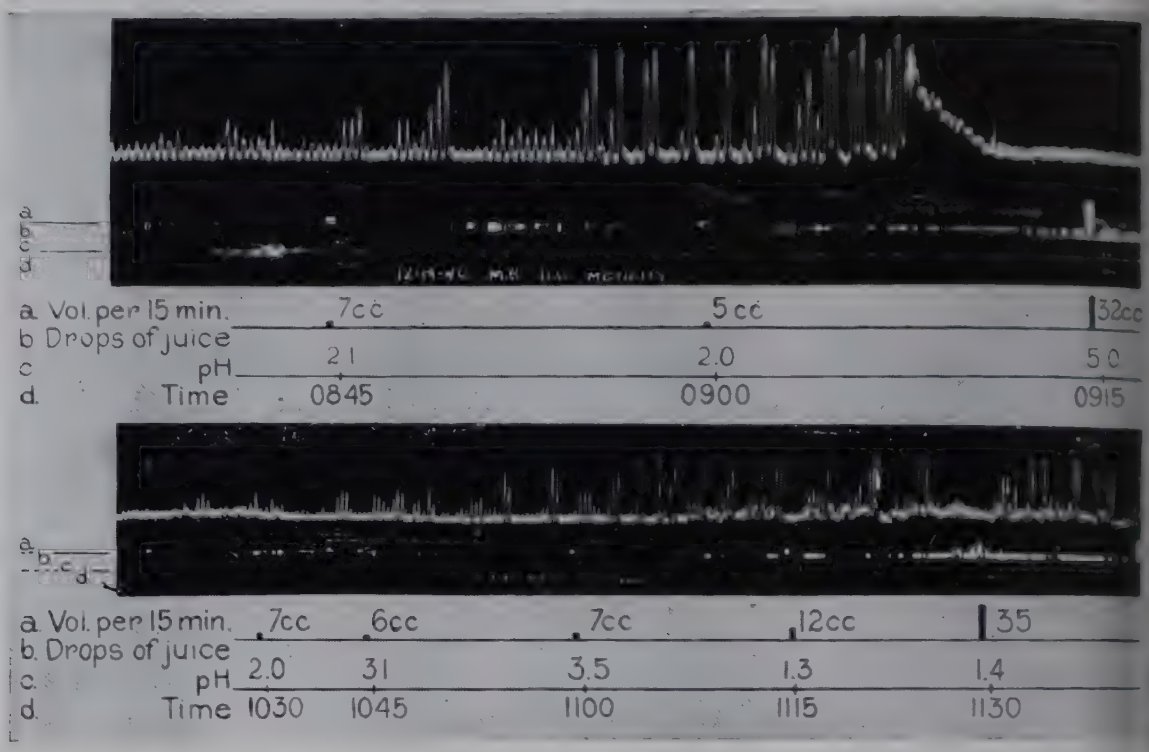


FIG. 108. A hunger period begins at 08:30 and subsides at 09:10. Because of copious flow of bile, the juice collected at 09:15 is high in volume but low i acidity. At 10:30 another motility period begins, and from its configuration appears that it is building up to a series of rapidly successive contractions, as i previous hunger periods. At the predicted onset of the most active motility phas an interview is started involving the arousing of anxiety and resentment. Th appears to be accompanied by either: (1) an inhibition of motility, with the co tractions breaking through intermittently and continuing to do so throughout t interview, while the secretory activity nevertheless increases progressively; or (an augmentation or prolongation of the motility, which would normally ha subsided not later than 11:15, with a concomitant augmentation of secretion.

identify any "typical" pattern; each patient reacts as an individual. T time intervals and the volume and pH of the secretion are redrawn bel each tracing to make them visible. Obviously it would require many m careful experiments to allow a satisfactory interpretation of these servations. To date, we have not been able to convince ourselves that can demonstrate any consistent augmentory effects of conscious emotio states on gastric motility.

Recently, Quigley et al. (45) were unable to establish any support the contention that pylorospasm may be produced by conscious emotio states. In their observations, emotions retarded gastric evacuation causing an inhibition of the pyloric sphincter region.

COMMENT. The evidence in support of the second premise of psychosomatic theory, viz., that certain emotions may be associa with hypermotility and hypersecretion, is suggestive but by no me conclusive.

Relation of Hypermotility and Hypersecretion to Peptic Ulcer

Almost all observers are agreed that excessive secretion *per se* cannot be the sole cause of peptic ulcer; a constitutional substrate or "diathesis" or predisposition appears to be a required factor. This conclusion is based on numerous observations in animals and man.

Hypersecretion and Peptic Ulcer in Experimental Animals. It has been demonstrated that peptic ulcer, particularly duodenal ulcer, may be produced in dogs under conditions of hypersecretion. Whether the conditions are comparable to those present in human peptic ulcer patients is conjectural. It now appears that, although some duodenal ulcer patients may secrete comparable amounts of acid, it is certain that many ulcer patients do not (p. 694).

The report of Silbermann (46) is frequently referred to (18, 23, 25) as an example of the production of peptic ulcer in dogs under conditions simulating those present in duodenal ulcer patients. It is difficult to accept his work in view of the undocumented evidence presented and of the fact that none of four subsequent groups of investigators have been able to confirm his report (47–51). Recently we have produced erosions and ulcers by shamfeeding esophagostomized dogs every hour or two in the fasting state.

Hypersecretion and Peptic Ulcer in Humans. The question whether ulcer patients manifest an excessive fasting gastric secretion before the lesion develops or during periods when the ulcer is healed has never been settled (Chap. 19, p. 701).

At present, then, the third assumption of the psychogenic theory of peptic ulcer still remains to be established.

Discussion

We have had sufficient experience with peptic ulcer patients to appreciate the important role played by anxiety and the associated unhygienic dietary habits in the genesis of ulcer. Accordingly, repeated attempts have been made in our laboratory to produce in dogs a hyperactivity of the stomach similar to that observed in some ulcer patients.

One of our approaches (52) to this problem was based on Pavlov's demonstration that if a pain stimulus be associated with the giving of food, the usual inhibitory effect of the pain on salivary secretion eventually disappears, and the pain stimulus may even become a conditioned *excitor* of salivary secretion. Pavlov's interpretation of this phenomenon was that: "the stimulation which entered into the center for defense reac-

tion now passes over to the food center" and that "there is merely a transference, an alteration of direction, an attraction of energy from one center to another." It will be recognized that this is not essentially different from the psychoanalytic interpretation of the psychic origin of somatic symptoms; viz., that repressed emotional energy overflows into the vegetative centers.

We attempted to apply the above principle to the gastric musculature. It was hoped that by training dogs not to manifest inhibition of hunger motility on pinching or pricking the skin a conditional hypertonus might eventually be produced. Experiments were carried out on six dogs. The results indicated that while the inhibitory unconditional reflex could be extinguished, it could not be reversed. The process of extinction of the inhibitory hunger-motility reflex, unlike that of the excitatory salivary-flow reflex, did not appear to lead to the excitation of a closely correlated unconditional excitatory motor center (vagus center in this instance).

It may be that in order to obtain hypermotility of the stomach by a conditional process, it would be necessary to approach the stomach through the vagal or predominant unconditional excitatory reflex mechanism. This would be difficult because the only known approach of this kind is via the vomiting center. Although the tonus of the vagal center is augmented in hunger, the augmentation is probably not reflex in nature. In sleep, the tonus of this center is also increased but it is not clear how a hypermotility of the stomach during the waking condition could be produced experimentally by utilizing this mechanism.

Using a pharmacologic approach, it was attempted (53) to determine whether the production of a continuous hypermotility in dogs would lead to the development of the clinical type of peptic ulcer. In a group of animals injected every two hours for two months with pilocarpine, acute lesions of the stomach and duodenum were observed, but no chronic ulcers.

If, as Alexander postulates, the basic psychogenic disturbance lies in a conflict-situation rather than in conscious emotional tension, then it may never be possible to reproduce the appropriate psychic state in lower animals. This does not render the theory any less susceptible to physiologic investigation, however, because motility-secretion studies can be carried out clinically with considerable satisfaction, provided proper methods are employed. Such investigations would be particularly significant in connection with psychoanalytic treatment.

The first step in such an investigation would be to demonstrate, in a case of healed ulcer, that the stomach is constantly acting as though it were about to receive food, i.e., manifesting a degree of motility and secretion materially in excess of controls. Then, in psychoanalytic treat-

ents involving the interpretation of dreams, it should be possible to ow how the gastric activity subsides as the disturbing emotion is ab-acted consciously and thus diverted from the nervous pathways leading the stomach.

Experimental neurosis has been produced in dogs, sheep, and rats. owever, in no instance has the occurrence of peptic ulcer been reported. a study of the pathway for the mediation of vibratory sensation, we pt three neurotic dogs for six months without ulcers appearing. How-er, their anticipatory anxiety was present for not more than a few hours ch week.

A Suggestion Regarding Terminology

The stimulation of gastric secretion by emotional states acting over e vagal pathway has often been termed a type of "psychic" secretion. ad this term not been applied already to another definite physiologic henomenon, there would be no objection to such usage. However, inas-uch as another mechanism of secretion is frequently designated by this rm, confusion and ambiguity result from applying it to the more recently scribed phenomenon. The term "psychic" secretion has become firmly oted in physiologic literature as a designation for the secretion of gastric ice by the vagal reflex mechanism in which the sight or thought of food n the presence of appetite) is the stimulus. This is the original sense in hich the term was used by Pavlov.

After it had been demonstrated that gastric secretion in response to am-feeding could occur in the absence of the cortex, it was proposed that e term "cephalic" phase of gastric secretion be used to designate secre-on which occurred in response to stimuli acting in the region of the ad. The latter term includes, then, the psychic and appetite secretion Pavlov as well as any secretion which may occur when stimuli (food) t in the region of the head but in the absence of cortical participation.

A number of considerations have convinced us of the need for a ecific term to denote the change in gastric function associated with notional states. In the first place, in going over the literature, we soon came aware that there is no way of knowing, when a paper bears the rm "psychic effects" in its title, whether it deals with "appetite" cretion or emotionally affected secretion. Furthermore, in our work on stric function in ulcer patients, we try, when the circumstances permit, induce anxiety or resentment in a patient by letting him overhear one d of a prearranged telephone conversation in which we appear to be fending him from criticism by a doctor or nurse. If, subsequently, there ppears an augmentation of secretion, we ask the patient what he is inking about. If it turns out that he has been wondering how much

longer the "test" is going to run because it is getting near noon and he is thinking about lunch, we realize that he is probably having psychic secretion, but not the kind of psychic secretion we are trying to produce. Sometimes we can spend all morning in conversation with the patient, exploring various aspects of his history or his environmental circumstances, without getting a "rise" out of his stomach, until finally he begins looking at his watch and trying to twist his head around to see how the motility tracing looks. If a period of gastric activity ensues, we are not certain whether it is psychic in that the conversation in itself or the subject matter have made him resentful, or whether it is psychic in the Pavlovian sense due to the proximity of the lunch hour.

We (54, 55) therefore proposed the term *emotogenic* to designate changes in gastric secretion and motility which occur as a result of certain affective states unrelated to the taking or the conscious thought of food. This term makes it possible to express more conveniently the probable mechanism of those alterations in gastric activity which are mediated by nervous pathways.

Two further examples will be presented briefly to illustrate the use of the term. A decrease in gastric secretion associated with distaste or disgust for food which has an unpleasant odor or appearance is a psychic inhibition, whereas a decreased secretion associated with sorrow, fear, or any emotion not related to food is an emotogenic inhibition.

The second example involves a more finely drawn distinction. A period of elevated motility and secretion while a patient is sleeping is always of interest to us in view of the possible association with a dream. We always awaken the patient during or immediately after such a period to ask him whether he was dreaming, and if so, what was the content of the dream. Occasionally the dream concerns food and the question arises whether the gastric activity is psychic, i.e., associated with the thought of food, or whether it is emotogenic, i.e., associated with an unconscious emotional conflict symbolized by food. Obviously, a dream of eating may be experienced by an individual who has no emotional conflict relating to or symbolized by food or eating. A person who does not get enough to eat is constantly preoccupied during his waking moments with thoughts of food; if he dreams of food, it is most likely a carryover of his conscious thoughts. In this case, an increase in gastric activity during the dream would most reasonably be considered psychic.

But in working with ulcer patients, we are dealing with the possibility raised by Alexander's theory, namely, that a dream of eating may be a symbol of the unconscious wish to be fed. Such a dream seemingly has no relation to the conscious thought of, or desire for, food because the ulcer patients under our observation are getting three meals and three interval

feedings. Yet the conscious factor may enter in; ulcer patients are usually on a restricted diet and often express a longing for a juicy steak (fried in onions, as a rule). It seems that the nature of the food dreamed about might offer a clue as to whether an associated increase in gastric activity is psychic or emotogenic. Here is an example:

O.S., a 39 year old salesman with a 10 year history of duodenal ulcer, had been boarded out with relatives at the age of seven, following the death of his mother. Throughout his childhood and adolescence he was tolerated, not loved. Of those years he has many bitter recollections, few pleasant ones.

During a motility and secretion study, while the patient was asleep, an atypical and unpredicted period of gastric activity occurred. Upon being awakened, the patient related a dream of a man in a white uniform tending a fruit stand at a busy intersection.

The "busy intersection" is a well chosen symbol of our laboratory, and the significance of the "man in white" dispensing food seems obvious. Since fruit is not what a hungry man generally pictures when he thinks of eating, we presume that the food in this dream may symbolize the emotional conflict-situation postulated by Alexander. If so, and if the observed gastric activity was indeed related to the dream, we would be inclined to interpret this as an emotogenic hyperactivity of the stomach.

Summary

Much circumstantial evidence indicates that psychic factors play a role in initiating the onset or recurrence of peptic ulcer. We believe that there is ample evidence to show that perforations and hemorrhages from peptic ulcer are increased in number when a population is exposed to an environmental situation of which sustained anxiety is an outstanding component. We believe the evidence warrants the presumptive conclusion that psychic trauma is an excitatory cause of peptic ulcer in ulcer-susceptible persons. Since peptic ulcer can still occur in man, the dog, and the rabbit after the vagus or splanchnic nerves are cut, it would appear that emotional factors that use these pathways can operate only as an excitatory and not as a basic cause of peptic ulcer.

The psychosomatic theory of peptic ulcer has not received the quantitative research attention it merits, regardless of whether it may prove to be only an excitatory cause. Better controlled clinical investigations of changes in gastric and duodenal motility and of secretion and blood flow accompanying temporary and prolonged affective states are feasible and desirable. It is on the basis of such well controlled, objective data that the psychosomatic theory will stand or fall.

The term *emotogenic* is recommended to designate the changes which occur in response to or associated with affective states.

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UTLINE OF CHAPTER 19

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CHAPTER 19

Pathologic Physiology

Introduction

Prior to the development of radiologic methods for demonstrating peptic ulcer, diagnosis of the disease was dependent to a considerable extent on tests for some characteristic disturbance in the function of the upper digestive tract, particularly gastric secretion. It is probable that if the present-day technique of roentgenologic visualization of ulcer craters and deformities had been available in the 1890's, much less attention would have been directed toward the quest for clinical tests to indicate the presence of an ulcer. Today, our interest in the pathologic physiology of peptic ulcer is motivated principally by an effort to gain a further understanding of the etiology and treatment of the disease.

Therefore, we shall not occupy ourselves in this Chapter with any discussion of the diagnostic value of gastric secretory response to test-meals or of the comparative merits of various methods of fractional analysis. We are not concerned, for example, with the question of whether a certain secretory curve in response to histamine, or alcohol, or caffeine is diagnostic of duodenal ulcer, but rather with the question *if and why* duodenal ulcer patients tend to secrete more than "normals" to these stimuli. In our opinion, any further development of fractional analysis should be in the direction of (a) identifying the "ulcer-susceptible" individual, (b) distinguishing between the "active" and "inactive" stage of duodenal ulcer in those instances where x-ray examination shows deformity but no demonstrable crater, and (c) evaluating the effectiveness of antacids.

Furthermore, the disturbance in function and, to a considerable extent, the symptoms of peptic ulcer are dependent on the site of the lesion; we will therefore discuss duodenal ulcer first and in greater detail, since (a) it is the more prevalent form of the disease and (b) the symptoms and altered physiology are usually typical. Gastric ulcer will then be taken up briefly.

Normal Variations in Secretory Response of Stomach to a Stimulus

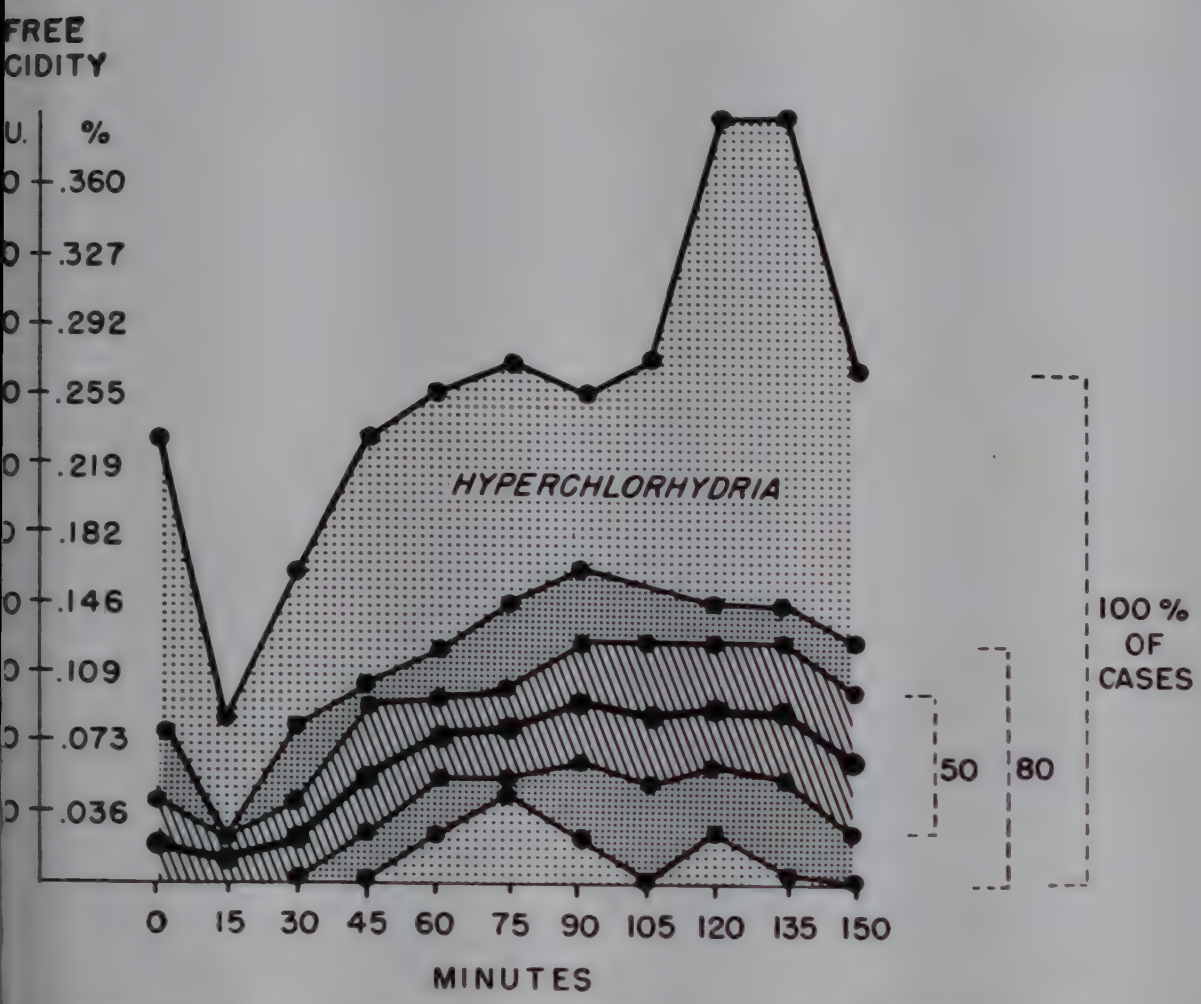
It is appropriate to discuss the normal variations in the secretory response of the stomach to a stimulus because it may yield evidence indicating that the stomach of peptic ulcer patients secretes an excessive amount of acid. In order to do this, we must possess acceptable standards of normality.

Bennett and Ryle (1) were probably the first to give statistical attention to the variations in the response of the stomach of the normal asymptomatic person to a test-meal by the method of fractional analysis. Their observations confirmed those of Rehfuss, Bergeim, and Hawk (2) in demonstrating that there is no curve of response specific to an asymptomatic person. The response, like all physiologic functions, was found to vary within a rather large range.

The range of variation found by Bennett and Ryle is illustrated in Fig. 109. The lined area encloses the curve of *free* acidity of 50 per cent of the subjects. The line in the center of the lined area represents the curve resulting from the average of all the data. The area covered by the lined area plus the heavy dotted one encloses the curve of free acidity of 80 per cent of the subjects. This is arbitrarily referred to as the "normal zone." The light dotted area below and above the "normal zone" represent the extremes or the unusual low and high values of the response of the stomach of the asymptomatic person.

The range of the response in the subjects of Bennett and Ryle covered almost the complete possible range of acid value, namely, from zero to approximately 166 clinical units or 0.56 per cent acid. The secretion of the parietal cell has an acid concentration of approximately 166 clinical units. If these cells form no acid, the acidity of the gastric contents will be zero. If parietal secretion is formed, the acidity of the gastric contents will depend on the amount of secretion formed in relation to the dilution and the neutralizing capacity of the nonparietal secretion and the gastric contents.

When a value which measures a function of the body falls into the extreme zones of the normal range, the chances of the organ being or becoming abnormal or of the function interfering with another body function are proportionally increased. Since symptoms may occur in association with anacidity or a high normal acidity, it is appropriate to attempt to associate the symptoms with the degree of acidity of the stomach. In doing so, some arbitrary limits are set for the purpose of quantitative comparison. In setting such a limit in the absence of specific knowledge which defines the limits of a "safe zone," it is most reasonable



IG. 109. Range of free acid response of 100 asymptomatic young male subjects to a gruel test-meal.

Hyponormal free acidity range at 1 hr. = 0 to 7.5 C.U.
Normal free acidity range at 1 hr. = 7.5 to 35 C.U.
Hypernormal free acidity range at 1 hr. = over 35 C.U.

The test is performed as follows: Add 30 Gm. of oatmeal to water and boil so nal volume is 450 cc. Add salt to taste and filter through gauze. This is drunk owly and then 10 cc. samples of the gastric contents are withdrawn every 10 inutes. It is well to withdraw 20 cc., reinject, and then withdraw 10 cc. in order o improve mixing. (Redrawn from Bennett & Ryle: *Guy's Hosp. Rep.*, **71**:286, 921.)

o set the limit where it has some statistical or mathematical meaning. In etting such a limit, sometimes the middle 50 per cent of cases (the mean lus or minus one probable error) is chosen, sometimes the middle 68 per ent (one standard deviation), and sometimes the middle 80 per cent (the ean plus or minus two probable errors) or the middle 95 per cent (the ean plus or minus two standard deviations). Bennett and Ryle, after onsulting Professor Karl Pearson, an eminent statistician, selected the niddle 80 per cent of cases to represent the "normal zone" or normo-hlorhydria. The remaining 10 per cent at either extreme are most likely

to develop symptoms due to achlorhydria or hyperchlorhydria. Vanzant, et al. (3) also chose the middle 80 per cent of cases to present when they statistically analyzed the values for acidity at one hour using a carbohydrate Ewald meal (Fig. 110).

Polland (4) has set up standards for the gastric secretory response to 0.1 mg. of histamine dihydrochloride per 10 kg. body weight. The stomach is emptied, the histamine given subcutaneously, and then the stomach is emptied every 10 minutes. The 10 minute specimen having the highest

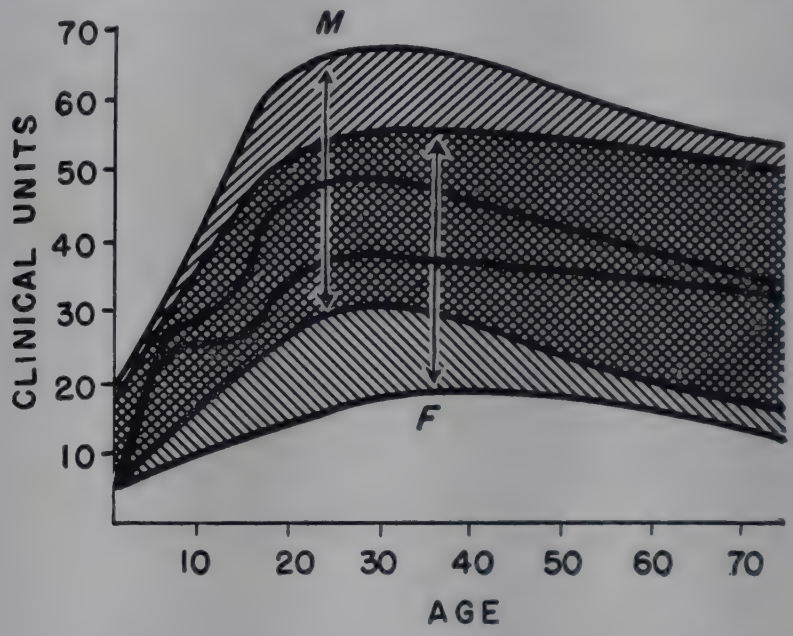


FIG. 110. Acidity values at one hour with Ewald test-meal. The arrows indicate the limits within which lay 80 per cent of the values at various decades of age for the two sexes. (Data of Vanzant et al.: *Arch. Int. Med.*, **49**:345, 1932.)

acidity is taken as the representative specimen. Some of the data normal subjects below 50 years of age is shown in Fig. 111. It should noted that the volume response of the males and females confo approximately to a normal distribution; this is not true of the acid c centration of the males, which is skewed to the right.

Ihre (5) has also set standards using the same dose of histan employed by Polland. He defined hypersecretion as the secretion of n than 180 cc. of juice in one hour, since more than 180 cc. exceeded standard deviations (95 per cent of the cases) beyond the mean.

Any of these methods is satisfactory for ascertaining whether duodenal or gastric ulcer patient varies significantly from a non-u subject regarding the response to some stimulus of gastric secretion. response to the alcohol or to the caffeine test-meal may be used.

portant points are to adopt a procedure, use it uniformly, and apply to both non-ulcer and ulcer subjects, giving attention to the age and x of the control and ulcer groups. Then the differences observed should e examined by a statistical method to ascertain if they might be due to ance or random sampling. The great difficulty with the literature aling with this subject is that the authors do not state the method used what constitutes the limits of the normal range.

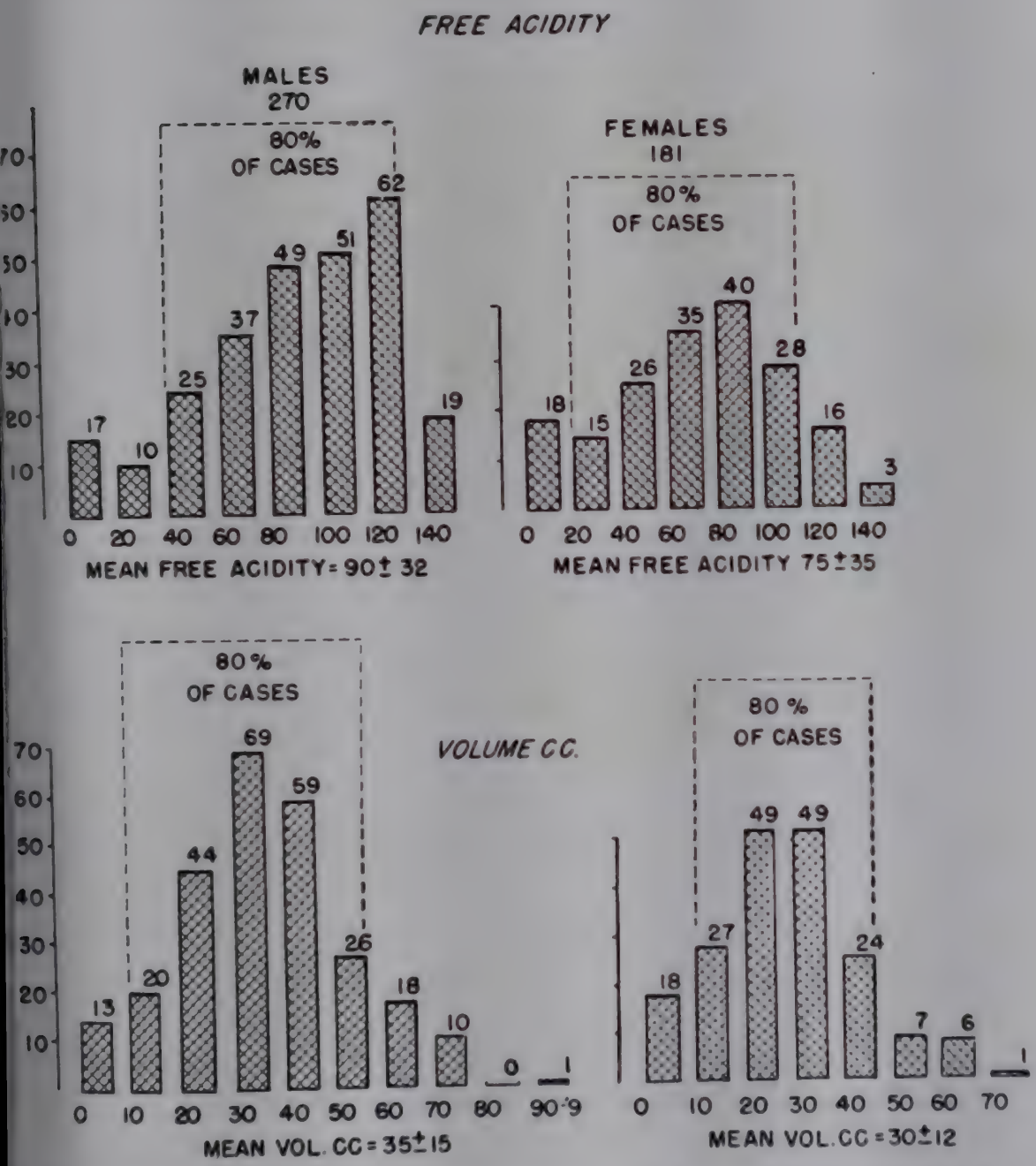


FIG. 111. Frequency distribution of responses to 0.1 mg. of histamine dihydroloride per 10 kg. of body weight. The values represent the maximal volume and id concentration attained during a 10 minute period. (Data of Polland: *Arch. Med.*, **51**:903, 1933.)

Pathologic Physiology of Duodenal Ulcer

Secretory Changes in the Stomach and Duodenum

Response to Stimuli

Regardless of the stimulus and the method of collecting specimens, there is general agreement regarding two points.

First, duodenal ulcer patients tend on the average to secrete gastric juice both in regards to volume and acidity than normal s Gastric ulcer patients do not tend on the average to secrete more juice than normal subjects. In the case of duodenal ulcer patie number manifesting hyperchlorhydria, according to any defini usually found to be significantly greater than is found in a n group of subjects. In some reports on gastric ulcer (2, 6), the mean

Table 113

Showing Incidence of Hyperchlorhydria in Response to a Test-m Normal Subjects and in Patients with Duodenal and Gastric U

Author	*Normal*			*Duodenal Ulcer*			*Gastric*	
	No. Cases	*No. Cases Hyper.*	*Per Cent Hyper.*	*No. Cases*	*No. Cases Hyper.*	*Per Cent Hyper.*	*No. Cases*	*No. Cases Hyp*
Barford (8)	100	8	8	114	66	58	..	..
Hurst & Venables (10)	...	..	..	...	...	..	53	17
Bockus et al. (9)	...	..	..	200	168	84	..	..
Ihre (a) (5)	41	0	0	204	70	35	69	7
Ihre (b) (5)	41	5	12	204	105	51	69	15
	Normal			*Peptic Ulcer*				
Polland (4)	384	92	24	148	68	46	—	—

Criterion of Hyperchlorhydria

Barford: Hyper.: 58 + C. U. free acid with gruel meal 1.5 hr.

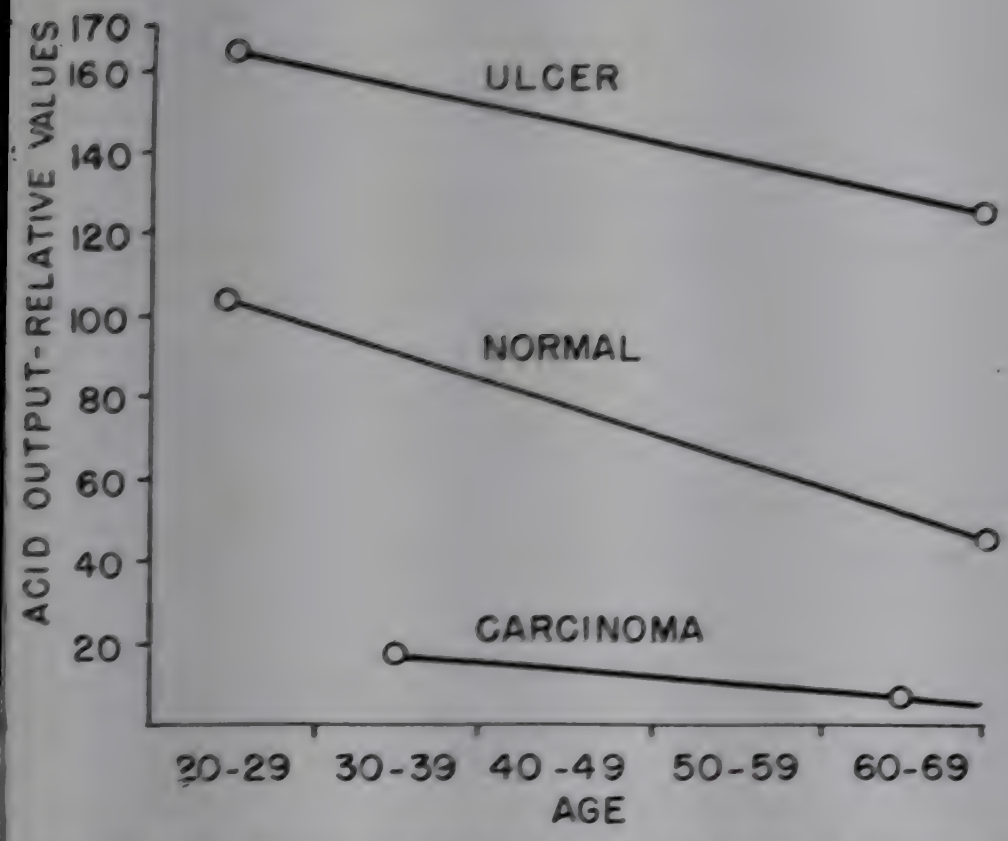
Hurst & Venables: Ditto.

Bockus et al.: Hyper.: 50 + C. U. with bread and water meal 1 hr.

Ihre (a): Hyper.: More than 180 cc. hr. in response to 0.1 mg. histam chloride per 10 kg. body weight.

Ihre (b): Same data adjusted so that more than 160 cc. hr. is conside hypersecretion.

Polland: Hyper.: More than 60 cc./10 min. period.



. 112. Showing relative total hydrochloric acid output in normal subjects, ts with peptic ulcer, and patients with gastric cancer in response to his-. The value for normal subjects at age 20–29 is set at 100 for purposes of rison. (Redrawn from Polland: *Arch. Int. Med.*, **51**:903, 1933.)

by either the histamine or Ewald methods is less than the mean for rmal group (4–13). It is difficult to compare the data in the litera- ecause of a lack of agreement on methods and because some authors t present all the data necessary for a comparison. Table 113 repre- n attempt to compare some of the data in the literature. It has been perience that the most striking differences between the response of ts with duodenal ulcer and of normal subjects are seen when the cid output is used (11), as it can be when the alcohol, the caffeine, ef bouillon, and, particularly, the histamine test-meals are used, the ormer by the "block method" (3). The difference between the mean cid output (volume × acidity) of ulcer patients and normal sub- n response to histamine is shown in Fig. 112.

cond, the overlap between the gastric secretory response of the nal ulcer subjects and the normal subjects is so great that it cannot d that the difference in acid secretion alone can account for the ce of the ulcer. This statement applies especially to patients with ulcer, where it is not uncommon to find hypochlorhydria or lity to an Ewald meal.

It is of importance that women have peptic ulcers at a lower leve of acidity than men. The data presented by Vanzant (p. 690) show tha female peptic ulcer patients in all age groups have a lower acidity i response to an Ewald test than the male ulcer patients, although we above the normal female group. This was confirmed by Perman (14 This observer also found that women had both gastric and duodenal ulce at a level of acidity well below that of the males. The sex difference ulcer patients in gastric secretory response also holds true for th response to histamine, as observed by Brown and Rivers (15). This se difference probably represents the same biologic difference in respon which occurs between normal males and females. The lessened gastr secretion of the normal female is further diminished in pregnancy (16 and probably also represents a further accentuation of the normal biolo sex difference. This diminished gastric secretion may account for t remission of peptic ulcer during pregnancy. However, the possibil should be borne in mind that the progesterone of pregnancy may pl a role in these remissions because of the relaxing effect of progesterone smooth muscle.

Basal Secretion of Acid

It is surprising how little data is available comparing the postabso tive continuous secretion in duodenal ulcer patients and in norm Although the fasting residuum in these patients has generally been fou to be hypernormal in acidity, or volume, or both (16, 17), the significa of such observations has certain limitations. A better procedure is study of the basal secretion (18–20). Bloomfield et al. (21) observed st ing differences between normal persons and duodenal ulcer patients w the total juice was collected over successive 10 minute periods for an h or more until a steady level of secretion was reached. In their experie many duodenal ulcer patients secrete basally a larger volume of juic higher acidity than is ever attained in asymptomatic normals (Fig. 1 In 75 people without evidence of organic disease of the stomach, concentration of total acid varied from a few degrees up to 97; in 26 c of duodenal ulcer, basal acidity of over 100 was found in 14. In the no group, the highest volume output was 15 cc. per 10 minute period; c of the ulcer group secreted more than 20 cc. per 10 minute period. Po et al. (22), in repeated fasting aspirations of three to four hours dur in some 20 duodenal ulcer cases, observed basal volumes correspon to those reported by Bloomfield, but the basal acidity values r exceeded 80 units.

Kellermann (20) and Hellebrandt et al. (23) made the impo observation that the level of basal secretion parallels the level of dig

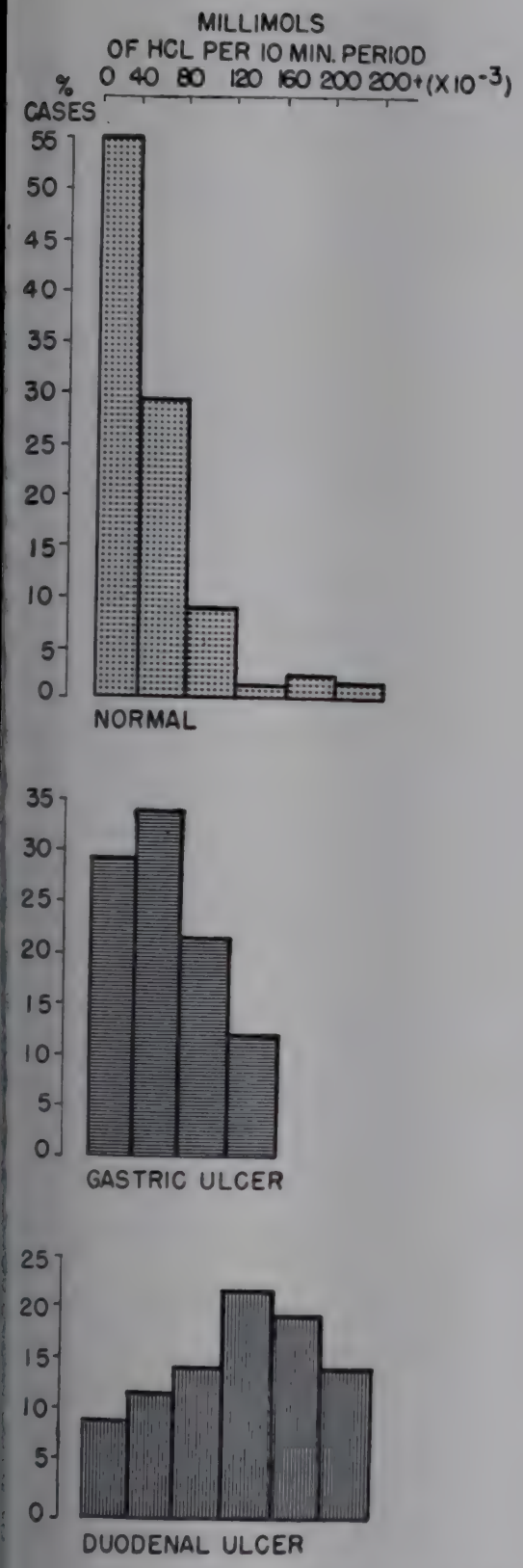


FIG. 113. Frequency distribution of highest acid output (volume × concentration) per 10 minutes during a basal secretion test in normal persons and patients with ulcer. Note that 84 per cent of normal persons and 63 per cent of gastric ulcer patients secrete less than 80×10^{-3} millimols per 10 minutes whereas 80 per cent of duodenal ulcer patients secrete more than this amount. (Data of Bloomfield, et al.: *J. Clin. Investigation*, **19**:863, 1940.)

cretion. Berk et al. (24), while studying the relation of the fasting gastric cidity to the acidity in the duodenal bulb, aspirated samples of morning cretion at 10 minute intervals for 30 minutes. The average pH of the astric contents was 1.62 in cases of active duodenal ulcer as against 51 in normals. All samples aspirated from ulcer patients had a pH less an 3.5, while one third of the specimens obtained from normals were

above that pH. Some groups of gastric ulcer patients, however, may secrete less acid than normal subjects under basal conditions both during the day and night. The same may be true of the acidity of the secretion obtained in response to histamine (Table 113).

Nocturnal Secretion of Acid

Studies of night secretion were first made for the purpose of determining whether the stomach secretes in the absence of stimuli. Chalfen (25, 26) concluded, from aspirations at intervals during the night on nine patients, that the secretion normally diminishes until, at about 3:00 A.M., it is generally absent. The subjects of these experiments were ill and the results equivocal.

In 1932, Henning and Norpoth (27) published two graphs showing the results of hourly aspirations during the night. One graph, showing no free acid, was said to represent the normal, while the other, showing a high acidity throughout the night, was described as the type seen exclusively in duodenal ulcer patients. In the following year, the same authors (28), having performed further experiments, modified their conclusions somewhat. They found that 34 of 41 duodenal ulcer patients exhibited a continuous secretion of highly acid juice during the night, whereas all of the eight "normals" showed no nocturnal acidity. However, they apparently classified their controls on an arbitrary basis; i.e., if the individual did not secrete during the night, he was a control. If he did, he was classified as a "vegetative neurotic."

According to Hellebrandt et al. (23), a juice of higher average acidity is secreted during the night than during the day in healthy subjects. These authors did not publish any values for volume of secretion but stated that in one experiment the average rate was 88 cc. per hour for 17 consecutive hours.

Winkelstein's (29) studies of night secretion consisted of aspirations at two hour intervals from 7:00 P.M. to 7:00 A.M., the last meal having been taken at 4:30 P.M. The average acidity in 62 duodenal ulcer patients was markedly higher than in 20 controls, 45 per cent of whom did not yield any free acid during the night although all responded normally to a test-meal. Val Dez (30) performed single aspirations at 9:00 P.M., midnight, and 3:00 A.M. The average volume and free acidity obtained in seven duodenal ulcer patients were distinctly greater than the average for five normals; in the latter, gastric secretion, though small in amount, was always present. Cornell et al. (31) repeated the studies of Winkelstein (29) "because of the opposing views chiefly with reference to normals." They stated that patients with uncomplicated duodenal ulcer produced a large amount of highly acid secretion during the night, while normal

subjects showed little or no free HCl and specimens were difficult to obtain in most instances because of the small amount of night secretion.

Apparently, the first report of studies of the *continuously* aspirated night secretion was that of Mears (32). The gastric contents were removed by continuous suction for eight hours during the night. The average volume and acidity were higher in 15 patients with active duodenal ulcer than in 50 controls. However, some of these controls were by no means "normals," inasmuch as they were patients with digestive ailments other than peptic ulcer; furthermore, 60 per cent of the controls were women, whereas only two of the 15 ulcer patients were women. Dragstedt et al. (33) presented the results of continuous gastric aspiration from 9:00 P.M. to 9:00 A.M. on 11 duodenal ulcer patients prior to vagotomy. The volumes ranged from 780 to 1855 cc., with acidities ranging from 25 to 75 clinical units of free acid. Values subsequently reported (34) for non-ulcer patients were considerably lower, but this group cannot be regarded as a satisfactory control since it was comprised of patients with carcinoma of the stomach, carcinoma of the colon, and gallbladder disease.

The first systematic approach to the study of nocturnal gastric secretion was that of Sandweiss and his associates (35, 36). Moreover, their reports have the merit of presenting the data in detail. These investigators compared the night secretion of duodenal ulcer patients with that of normals in respect to both hourly aspirations and continuous suction. Moreover, they studied the effects on night secretion of the composition of the noon and evening meals taken prior to the periods of aspiration. They observed that there was considerable variation in the curves of night secretion from one "normal" to the next, from one ulcer patient to another, and on different nights in the same individual. Although the total number of persons studied was insufficient to allow statistical validation of the data, the following tentative conclusions were drawn: (a) A greater average volume of gastric contents may be aspirated at the end of each hour from ulcer patients than from normals. The total for eight nocturnal aspirations amounted to 300 cc. or more in 25 per cent of the ulcer patients, whereas not one of the normals yielded 300 cc. (b) The average volume and acidity of gastric contents obtained by continuous aspiration from midnight to 7:00 A.M. are approximately the same in duodenal ulcer patients as in normals. (c) Therefore, the greater volumes of night secretions observed in duodenal ulcer patients when intermittent aspirations are used are not due to more active secretion but to delayed emptying.

The most recent study of this problem failed to confirm Sandweiss et al. in regard to the continuous secretion. Levin et al. (37) measured the continuously aspirated gastric contents from 8:30 P.M. to 8:30 A.M.

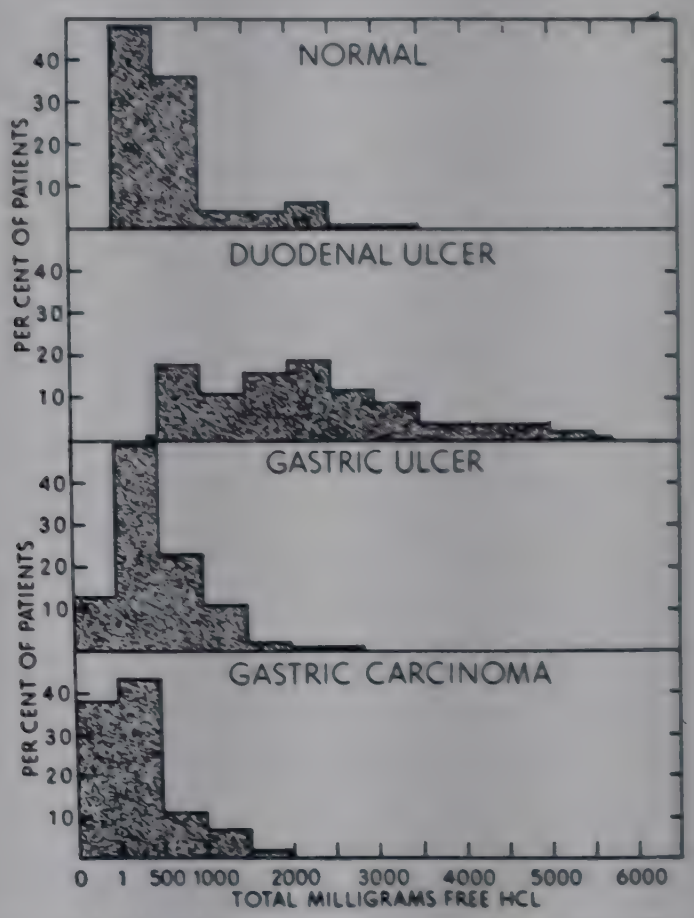


FIG. 114. Output of hydrochloric acid during the night. (Courtesy, Levin: *Arch. Surg.*, **56**:3, 1948.)

Table 114

THE AVERAGE VOLUME, FREE ACIDITY, AND MG. FREE HCL IN THE 12 HOUR NOCTURNAL GASTRIC SECRETION IN NORMAL INDIVIDUALS AND IN PATIENTS WITH DUODENAL ULCER, GASTRIC ULCER, AND GASTRIC CARCINOMA*

	Volume (Cc.)	*Free Acid (Clinical Units)*	*Mg. Free HCl*
Normal	581	29	661
Duodenal Ulcer	1004	61	2242
Gastric Ulcer	600	21	454
Gastric Carcinoma	483	14	245

* Levin et al. (164).

wing a late afternoon meal consisting of broth, orange juice, and
The results (Table 114 and Fig. 114) leave no doubt that the duo-
l ulcer patients usually secrete a greater volume, with a higher con-
ation of acid, than do the normals. Levin et al. found that about one
of the duodenal ulcer patients secreted a nocturnal volume greater
the highest volume attained by any of the normals. Going a step
er, only 4 per cent of the normals yielded a volume greater than
cc., whereas 47 per cent of the duodenal ulcer patients exceeded
amount. This demonstrates that some duodenal ulcer patients are
d hypernormal secretors. All of these patients were under treatment
cer distress at the time of these studies and in 70 per cent of the cases
ter was demonstrable by x-ray. Though there is overlapping in the
ne and acid secreted by the duodenal ulcer patients and the normal
cts, the difference between the two groups is statistically highly
icant.

OMMENT. The discrepancies between the results of Sandweiss' and
's groups may lie in the fact that the former studied ambulatory
nts while the latter performed their aspirations on people admitted
hospital for treatment. There was also a difference in the controls
, according to Levin et al., may have been important; the former
ooled all the specimens, which may have decreased the free acidity.
he disagreement is a salutary one, inasmuch as it points the way
d a properly controlled study. In contrast to preceding investiga-
Levin et al. attempted to obtain a control series comparable in age
ex to the ulcer group. Both the above groups of investigators stand-
ed the quantity and composition of food intake in the last meal pre-
g the aspirations. Comparisons between the two groups should be
on aspirations performed during the same season of the year. For
ple, all of Sandweiss' control determinations were made in the
r months, whereas more than half the aspirations on ulcer patients
performed in the months of June and July. It would be wise to
old alkalies for several days before the aspiration, because of their
le effect on gastric secretion. Automatic devices should not be
upon to provide continuous suction; an observer must be in con-
attendance to see that the stomach tube is not obstructed.

our opinion, the object of these experiments, viz., to determine
ner or not the duodenal ulcer patient is a hypersecretor, can be
ved just as readily by conducting studies on basal secretion during
renoon or afternoon rather than during the night. The volume of
g secretion between the hours of 7:00 or 8:00 A.M. and noon is
uate for the purposes of the study. In fact, Stein (38) demonstrated
a one hour continuous aspiration of the basal secretion is as reliable

a measure of the effect of vagotomy on interdigestive secretion as is continuous overnight aspiration (Table 115).

Table 115

COMPARISON OF HOURLY ACID OUTPUT DURING THE NIGHT AND DURING A ONE HOUR ASPIRATION OF BASAL SECRETION*

	Twelve Hour Continuous Night Secretion Output of Free HCl M. Eq./Hr.	*Basal Secretion One Hour Continuous Aspiration M. Eq./Hr.*
Control (22 patients)	3.9	3.7
Vagotomy (18 patients)	0.17	0.2
Per cent reduction in acid output	96	95

* Courtesy of Dr. Irving F. Stein, Jr.

It should be easier, under basal conditions, to minimize the regur tion of the duodenal secretions by aspirating these secretions separa but this may create abnormal conditions. We are at a loss to unders the significance of such statements as "when bile appeared in the aspi juice, the specimen was discarded." In our experience, if we were t card all of the bile-stained specimens obtained in our continuous hour aspirations, we would be throwing out many specimens and act covering up physiologic events. As far as we are concerned, a bil specimen obtained by seven to 12 hours of continuous nocturnal a tion would be the exception rather than the rule. Such aspirations not the volume of gastric *secretion*, of course, but the volume of g *contents*, which is of chief interest in these experiments. Bile-stained mens should be so labeled and then titrated like any other specim treating the data, they may be included or separated to ascertai significant difference is observed. They should not be discarded.

It is occasionally stated in the literature that even though the m of measuring gastric and/or duodenal function are not quantitative are adequate for purposes of comparing ulcer patients with n because the errors will affect both groups in the same direction and same extent. This assumption is not necessarily true and in our o more attention should be devoted to determining the relative ac of our methods and improving them.

Although, as the foregoing discussion indicates, more data on th gastric secretion of normal subjects and duodenal ulcer patients are n the preponderance of the existing evidence, like the evidence fro meals, shows that duodenal ulcer is usually characterized by hyp

on of acid. In our laboratory, it has been a consistent observation that uodenal ulcer patients yield a greater average total output of free acid ıan do controls of comparable age and sex in the fasting state. Is this ypersecretion due to the ulcer? The three avenues of investigation which ıight supply the evidence needed to answer this question have not, to our nowledge been pursued adequately. The three subsidiary questions hich need to be answered are:

1. Does a hypersecretion exist prior to the development of duodenal lcer? We are not aware of any report of a planned study designed to btain this information. Considering that at least 5 per cent of freshman ıedical students will develop duodenal ulcers by the time they are 40 ears old, it is obvious that a project of study embracing every medical hool which includes a qualified gastroenterologist on its staff should ıpply reliable evidence on this point within the next 20 years.

2. Does the hypersecretion of a duodenal ulcer patient persist after ıe ulcer has healed? In so far as this question refers to the response to lcohol, histamine, or caffeine, it may be answered in the affirmative. lowever, the evidence in the literature supporting this statement is rather ıeager. Hurst and Venables (10) reported a few cases in which the cidity increased after treatment. Bockus et al. (9) found no change in 2 per cent, an elevation in 43 per cent, and a decrease in 35 per cent, ifferences which are not statistically significant. Musick et al. (39), using ıe caffeine test-meal, found no clear difference in response between a roup of patients in a remission and a group with the active disease. elario (40), using an Ewald test-meal, found that in those peptic ulcer atients with no symptoms on a second examination, 70 per cent had the ıme or lower acidity and 20 per cent a higher acidity; in those with mptoms, 15 per cent had a lower acidity and 85 per cent a higher acidity. his report cannot be evaluated because of lack of details such as his efinition of what constituted changes in acidity. Brown and Dolkart (41) llowed 15 duodenal ulcer patients for three years with frequent Ewald st-meals and found no constant relationship between variations in cidity and recurrences of symptoms. Levin et al. (166) reported studies of octurnal secretion in duodenal ulcer patients before and after healing; ıere was no significant difference.

3. What is the effect of experimental peptic ulcer on gastric secretion? avlov (42) stated that an increased secretion of acid follows the spon- ıneous development of an ulcer in a Pavlov pouch. Since then, no decisive xperiments have been carried out, although there are a few reports on ıe subject. No consistent effect on secretion following production of an cute ulcer was observed by Hardt (43), whereas Dragstedt and Vaughn 44) reported an increase, but their data are not convincing. According to

Wolfer (45), the presence of a chronic gastric ulcer produced by x-ray di not alter the secretory curve; a similar observation was reported when th ulcer was produced by radium implantation (46). We (47) tried determine, by performing gastric analyses at weekly intervals, wheth the gastric secretion of Mann-Williamson dogs rises after jejunal ulc develops; however, the findings were equivocal.

The presence of an ulcer in the duodenum could theoretically cau increased acidity of the gastric contents by disturbing the normal phy ologic mechanism in several ways. (a) Delayed emptying due to duoden or pyloric spasm would increase the retention of acid secretions and pr long the gastric phase of secretion. (b) The presence of an ulcer m stimulate gastric secretion by causing the release of histamine-like su stances from the irritated tissues. (c) The normal inhibitory mechani operating in the duodenum to depress gastric secretion may be impair Nevertheless, clinical observations (16, 48–50) support the view th hypersecretion appears to be a characteristic of the individual predispo to duodenal ulcer; it precedes the ulcer and persists after the ulcer healed. If it does remain the same, *this is another point showing that the o and recurrence of ulcer is not due to acid but either to some decrease in local resist of the mucosa or to the introduction of some new exogenous aggressive factor.*

Secretion of Pepsin

Basal secretion of pepsin has apparently not been the subject special investigation. In a report by Mullins and Flood (51), the aver peptic activity of the fasting residuum in seven ulcer patients was proximately the same as that in a "miscellaneous group." In Ihre's experiments, the gastric juice during a 20 minute continuous fas aspiration period preceding the introduction of a stimulus showed same average concentration of pepsin for both normals and duod ulcer patients, but the latter secreted a volume twice that of the for Whether Ihre discarded the fasting residuum he does not state, but reasonable to assume that he did.

Polland and Bloomfield (53) reported that the concentratio histamine-stimulated pepsin output of ulcer patients fell within the range as the controls, whereas Helmer and Fouts (54) found tha patients with peptic ulcer, as well as in nervous and tense individuals pepsin concentration of the histamine-stimulated gastric juice may b to four times as high as in the normal. Vanzant et al. (55) observed the concentration of pepsin in either the fasting residuum or the secr to an Ewald meal was higher on the average in duodenal ulcer pa than in normals. Moreover, the concentration of pepsin varied in proportion to the severity of the disease. Patients in whom the ulce

en diagnosed previously but who had been symptom-free for a number years (duodenal cap still deformed) usually had pepsin values within e normal range, although the mean value was well above the normal erage. In moderate and severe cases, more of the pepsin values fell itside the normal range and the mean was 2.5 times that found in the dinary cases. The authors concluded that the determination of pepsin of more clinical value than the determination of acid, although neither of diagnostic importance because, in a group of 47 cases with ulcer mptoms but no ulcer, the acid and pepsin concentrations were distributed in much the same fashion as were those for the severe ulcer cases. Further investigations will obviously be necessary before the complete cture of pepsin change becomes fully apparent. The first point to be solved is whether the duodenal ulcer patient secretes a fasting juice of rmal peptic power, as Ihre's data show, or whether the concentration increased, as Vanzant et al. find. The second point is to demonstrate at the pepsin concentration has some etiologic significance, which, cording to very good evidence, it does not possess.

Secretion of Mucus

A comparison of the basal secretion of mucus in ulcer patients and rmals has not been reported. Necheles and Coyne (56) studied the cretion of mucus in response to pilocarpine; they found that ulcer tients did not manifest the increase in mucous secretion after pilorpine administration noted in normal control subjects. Anderson et al. 7, 58), using 7 per cent alcohol as a stimulant for mucous secretion, ported that the concentration of mucus in the aspirated samples was arkedly lower in duodenal ulcer patients than in normal individuals. terestingly, they found that after treating the duodenal ulcer patients th a preparation of hog mucin administered orally for several months, concentration of mucin in alcohol-stimulated juice rose to normal els. The studies of Ihre (52) on the concentration of mucin in gastric ce stimulated by histamine or insulin-hypoglycemia failed to disclose ignificant difference in the values for normal persons and ulcer patients. accurate quantitative evaluation of the status of mucous secretion by mucosa of the upper digestive tract will not be possible until a dependle method is developed for the determination of mucus.

Duodenal Secretions

In contrast to the large amount of data in experimental animals on the ation of bile and pancreatic juice to peptic ulcer, very little information out these secretions in the human peptic ulcer patient is available. cClure (59) stated that about 25 per cent of patients with duodenal

ulcer show abnormal hepatic function as determined by analysis of du denal bile. He reported also that there is a tendency for ulcer patients manifest low values for pancreatic lipase in the duodenal contents. Lage lof (60) stated that the secretin test gives normal values in ulcer patien whereas Angier et al. (61) found the lipase reduced.

The best data on the pancreatic secretion in duodenal ulcer are the of Comfort and Osterberg (62). Using an Agren-Lagerlof tube, th aspirated the duodenal secretions by continuous suction. The findings 10 proven duodenal ulcer patients were compared with those in 10 healt subjects. In the fasting secretion, the range of values and the avera values for the volume of duodenal contents, concentration of bicarbona and concentration of trypsin were approximately the same in the t groups. The range and average values for the concentration of amyl and lipase were greater in duodenal ulcer patients than in normal perso In response to secretin, duodenal ulcer patients secreted a greater amou of amylase, trypsin, and lipase than did the normals, while the secret of bicarbonate was approximately equal. The authors could thus obt no evidence that pancreatic secretion is deficient in cases of duodenal ulc

As far as gallbladder function is concerned, Boyden and Berman demonstrated that the rate of gallbladder evacuation in response to yolks and milk is, if anything, more rapid in duodenal ulcer patients th in normals. Thus, there is apparently no deficiency in the delivery of into the duodenum following a meal of adequate fat content.

The special secretion elaborated by the first portion of the duoden (Brunner's glands area) has not been extensively studied until q recently. Florey and co-workers (64) have shown that this secretio produced in unexpectedly large quantities and is an important facto maintenance of normal duodenal pH. The secretion of Brunner's gl is controlled by several mechanisms. Probably the most important m anism is the hormonal; a very marked flow occurs in response to a n We (65) have studied the secretion of Brunner's glands in dogs with first portion of the duodenum transplanted under the skin. In resp to a mixed meal, as much as 14 cc. of mucoid fluid has been secret one hour by this tiny strip of intestine, only approximately one inc length. Another important mechanism for the stimulation of Brun glands is the direct action of HCl; this, however, may also be hormo transmitted. At present, it is not known whether a deficiency in Brunner's glands' secretion is present in duodenal ulcer.

Mechanism of Hypersecretion in Duodenal Ulcer

The possible nature of the secretory disturbance is to be sought a the follo ing: (1) *The secretory stimuli in the ulcer patient are normal in ty*

ey are acting to an excessive degree or the ulcer patient manifests an reased sensitivity to these stimuli. (2) *Some abnormal secretory mechanism sts in the ulcer patient.*

These two possibilities will be discussed before the two further possibili- are enumerated. As to whether the gastric secretory mechanism in ulcer patient is qualitatively the same as, or is different than, that a normal person, we must first deal with the question of whether we er truly attain basal conditions in our studies of fasting gastric secretion.

Evaluation of Evidence from Basal and Nocturnal Secretion udies. As we have shown, there is a disagreement in the literature as to ether a normal individual secretes acid in the fasting state. In so far as "fasting state" is defined as beginning from the time that the stomach mpty of its previous meal, it is not actually a stimulus-free period for gastric glands, because there is normally an intestinal phase of gastric retion. This phenomenon must be taken into account in evaluating the nificance of nocturnal secretion studies. If the night secretion in a mal individual falls progressively until the secretion ceases several urs after midnight, it may represent the termination of the intestinal ase. If, during the same period, the ulcer patient continues to secrete ively, then either: (a) he is manifesting an accentuated and prolonged ponse to a normal stimulus, i.e., the intestinal phase, or (b) some other nulus, not present in the normal individual, is operating in the duo- al ulcer patient. This latter stimulus may be one of two types, a dis- rge of impulses via the vagus nerves, according to the mechanism tulated by Cushing (66), or the release of histamine-like substances m the intestinal mucous membrane.

The evidence shows that the secretion continues throughout the night, l, according to Hellebrandt (23), it tends to be higher in a person who ps soundly than in one who does not rest well. If these observations present the facts, then those ulcer patients who secrete more than the mal subjects are hypernormal, not abnormal. Further speculation on significance of night secretion studies in relation to the possible chanisms of hypersecretion is unwarranted until further careful experi- nts are carried out to determine whether or not normal individuals rete throughout the night. We suspect that when all the evidence is in, will be found that there are some apparently normal persons who secrete night, some who secrete on some nights and not on others, and some o manifest a nocturnal anacidity.

If, on the other hand, the basal state is taken to mean complete mental, otional, and physical rest in the postabsorptive period, it should be sible to compare the gastric secretion in duodenal ulcer patients and trols in the absence of all known normal stimuli for gastric secretion.

Gordon and Chernya (67) are of the opinion that the only way to a plish this is under hypnosis in an individual with a gastric fistula. maintain that only under hypnotic suggestion can a person be place state of complete emotional tranquility and that only by having ac the gastric secretions via a fistula can the factor of mechanical stim of secretion by the tube be ruled out. In our opinion, a fistula pa unnecessary; the stomach tube does not stimulate secretion of acid main problem is to rule out psychic and emotogenic stimuli. N sleep will eliminate the psychic phase but not necessarily emot disturbance, inasmuch as the patient might dream. However, probable that if a sufficient number of observations are carried satisfactory evidence can be obtained. The results should help to mine whether an abnormal mechanism for gastric secretion exists hypersecreting duodenal ulcer patient.

Evaluation of Evidence from Atropine Studies. In studyi hypersecretion of Mann-Williamson dogs, we (68) observed th gastric secretory response to a meat meal was not abolished in thes by the same dose of atropine which abolished the response prepor (see p. 345). We suggested that an abnormal mechanism for secretion might be operating in these dogs, inasmuch as the reac atropine indicated that a part of the stimulus to gastric secreti histamine, or a histamine-like substance. We then turned to the li to see if there was any evidence upon which to base analagous ded concerning the hypersecretion in duodenal ulcer. We were surp find that there are many significant gaps in our knowledge of this mental subject, as the following summary will indicate.

The effect of atropine on gastric secretion in the dog is unequ established. One milligram subcutaneously (0.1 mg. per kilo body abolishes the normal interdigestive secretion and the gastric s response to a meal for from one to three hours (69–71). It abol phases of gastric secretion. The same dose produces a definite, but partial, inhibition of the response to histamine; the inhibition chiefly of a decreased total output of acid, the concentration remaining stationary or increasing slightly (72). However, th mode of action of atropine is uncertain. It undoubtedly acts to b action of secretory nerves (73). In addition, it is able to inhibit the response to histamine, a drug which presumably acts directly parietal cell (75). In both of these instances, it may be exerting usual action of blocking the action of acetylcholine on the effector the former instance, it blocks the phasic activity of the postganglio fibers, whereas in the latter instance it blocks the basal tonic ac these nerve fibers and thereby decreases their responsiveness to h

ine inhibits but does not abolish the secretory response to alcohol This indicates that alcohol releases histamine (75), and if histamine ormal humoral agent, then alcohol releases histamine by a different anism (irritation) from that concerned in the release of histamine by agogues in food, because atropine abolishes the gastric secretory se to secretagogues in, or arising from, food (76).

e study of the effect of atropine on human gastric secretion is beset certain technical difficulties and the interpretation of the results ed in the varied and extensive clinical studies must therefore be ached with circumspection. Unlike experiments on dogs with pouches, where the total secretion can be collected and measured, dies on humans the usual practice is to remove a fractional sample mixed gastric contents at intervals and to determine the acid con- ation of these samples. Not only does such a method give no measure total amount of acid being secreted (concentration × volume), but fails to reveal accurately what the secretory activity of the stomach he interval between two samplings. By such a method, it would be ifficult to detect a period of, let us say, one hour during which no c juice was being secreted because the gastric contents would bly contain some acid which had been secreted earlier. This applies ally when one considers that atropine tends to inhibit gastric ation.

e only studies in which complete drainage of the gastric contents nuously or at short intervals has been performed are those in which ol (77) or histamine (78, 79) have been employed as the stimulating As would be anticipated on the basis of the results obtained in the hese studies show that atropine partially inhibits the secretion of n response to these stimuli. Other difficulties in the interpretation results of investigations on human subjects are presented by such s as the dose of atropine employed and the interval between the istration of atropine and the administration of the stimulant. It is forgotten that atropine must be administered in an amount sufficient se physiologic symptoms (xerostomia and difficulty in accommoda- in order to insure full effect.

e few reports available on the subject (80–82) indicate that atropine hes normal interdigestive secretion in man, just as in the dog. How- additional data of this type are required before this can be con- d to be established. The report by Mears (32) indicating that the l interdigestive (nocturnal) secretion is not abolished by atropine e criticized on the grounds that the dose of atropine which he yed was not sufficient and the collection periods (two hours) were g to detect a possible short interval of abolished secretion. The

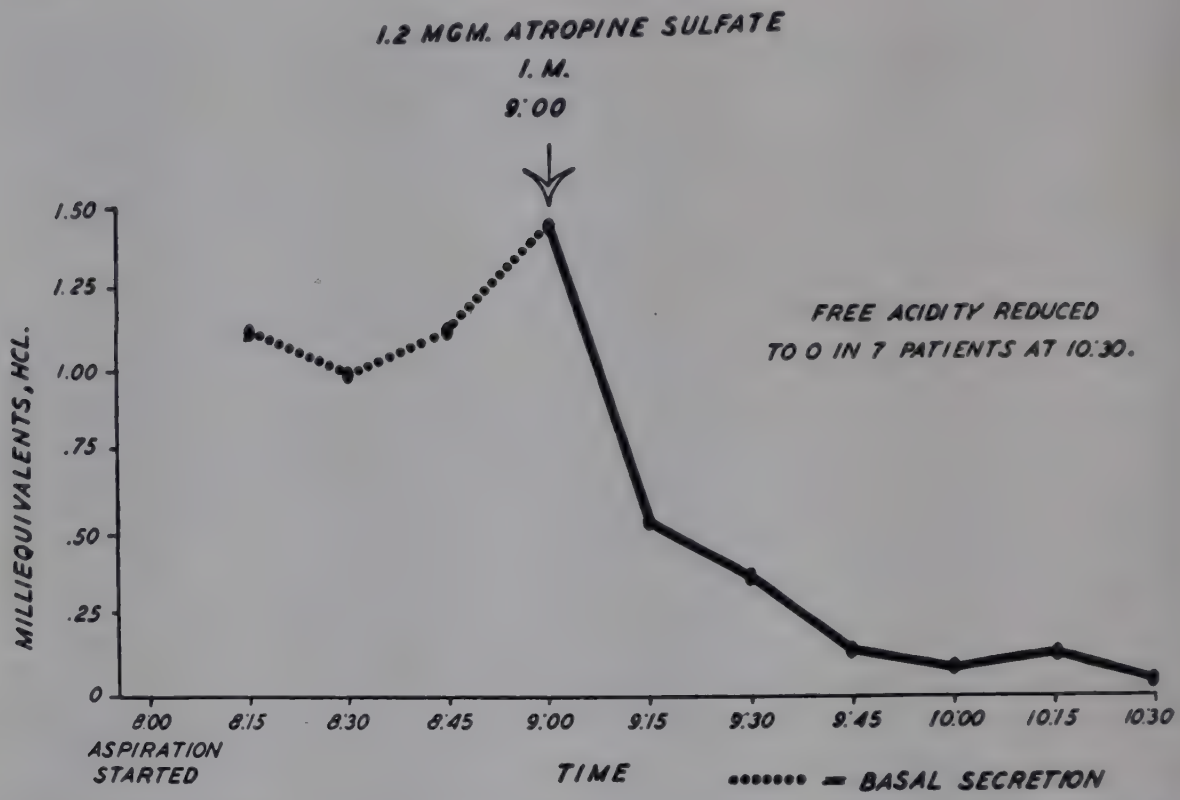


FIG. 115. Effect of atropine on gastric acidity in duodenal ulcer patients. (Stein & Meyer: *Surg., Gynec. & Obst.* **87**:188, 1948.)

reported failure of atropine to abolish the night secretion in the peptic ulcer patient appears to indicate that in these patients the secretion of HCl cannot be abolished by atropine; however, the work of Stein and Meyer (83) shows that in most duodenal ulcer patients the intramuscular injection of 1.2 mg. of atropine will temporarily abolish the secretion of free acid (Fig. 115). Kirsner and his co-workers (84) have found that in those ulcer patients who have exceedingly high fasting gastric secretory levels, doses of atropine as large as 2 mg. have little or no effect.

Does Atropine Abolish the Response to a Meal in the Human? Due to the difficulties in interpretation discussed above, no decisive answer to this question can be provided. The available evidence has generally been interpreted to indicate that the production of HCl in response to a meal is inhibited but not abolished by atropine (71, 85, 86). Inhibition does occur; whether this inhibition is complete during the period of maximum action of the atropine cannot be answered on the basis of the evidence available.

Inasmuch as it is uncertain whether atropine abolishes the normal interdigestive and meal secretion in man, the best we can do at present is to offer the following theoretical possibilities.

1. There exists in man a normal mechanism for gastric secretion in response to a meal which cannot be abolished by atropine. If this were

true, then it might be supposed that the failure of atropine to abolish interdigestive secretion in the ulcer patient is due to the abnormal activation of this process in the absence of food.

2. All phases of gastric secretion can be abolished by atropine in the normal man, just as in the normal dog. Then the failure to abolish the hypersecretion of ulcer with atropine would represent an abnormal type of stimulus, as in the dog.

3. Some normal individuals exhibit an interdigestive and meal secretion which cannot be abolished by atropine. Peptic ulcer cases would then represent exaggerations of this normal variation.

The nature of the mechanism in man causing gastric secretion which appears to be difficult to abolish with atropine is an interesting problem. There are two possibilities. The first possibility is that histamine is released, since ordinary doses of atropine do not abolish the action of histamine. The other possibility is drawn from an analogy with the effect of the parasympathetic nerves on the musculature of the stomach, colon, and urinary bladder. In these instances very large doses of atropine are required to abolish the action of the stimulation of the nerve on the musculature and even then may not do it completely.

Evaluation of Evidence from Action of Histamine and Alcohol on Gastric Secretion. Histamine is believed to act directly on the parietal cell. Alcohol is presumed to act by causing the release of histamine. The fact that the gastric secretory response to histamine or alcohol is usually greater in the duodenal ulcer patient than in the normal person may mean that (a) these patients are particularly sensitive to histamine, or (b) histamine is constantly being formed in amounts adequate to stimulate a considerable secretion of acid in the fasting state, or (c) histamine acts by potentiating some other agent responsible for gastric secretion, e.g., acetylcholine, which is being formed excessively in the ulcer patient. A synergistic or potentiating mechanism is suggested by the observations of Stein and Meyer (83), who reported a considerable decrease in the acid response to histamine following vagotomy (Fig. 116). Since histamine-stimulated juice is known to be weak in peptic power as compared to pilocarpine-stimulated juice, studies of the fasting concentration of pepsin in duodenal ulcer patients may help shed some light on the role of histamine in hypersecretion.

Evaluation of Evidence from Caffeine Studies. The results of our investigations on caffeine (Chapter 11) indicated that hypersecretion in ulcer patients may be explained in part on the basis of a synergistic relation between two or more mechanisms of gastric secretion, such as between caffeine and histamine. Since in normal subjects the simultaneous administration of caffeine and histamine results in a secretory curve similar to

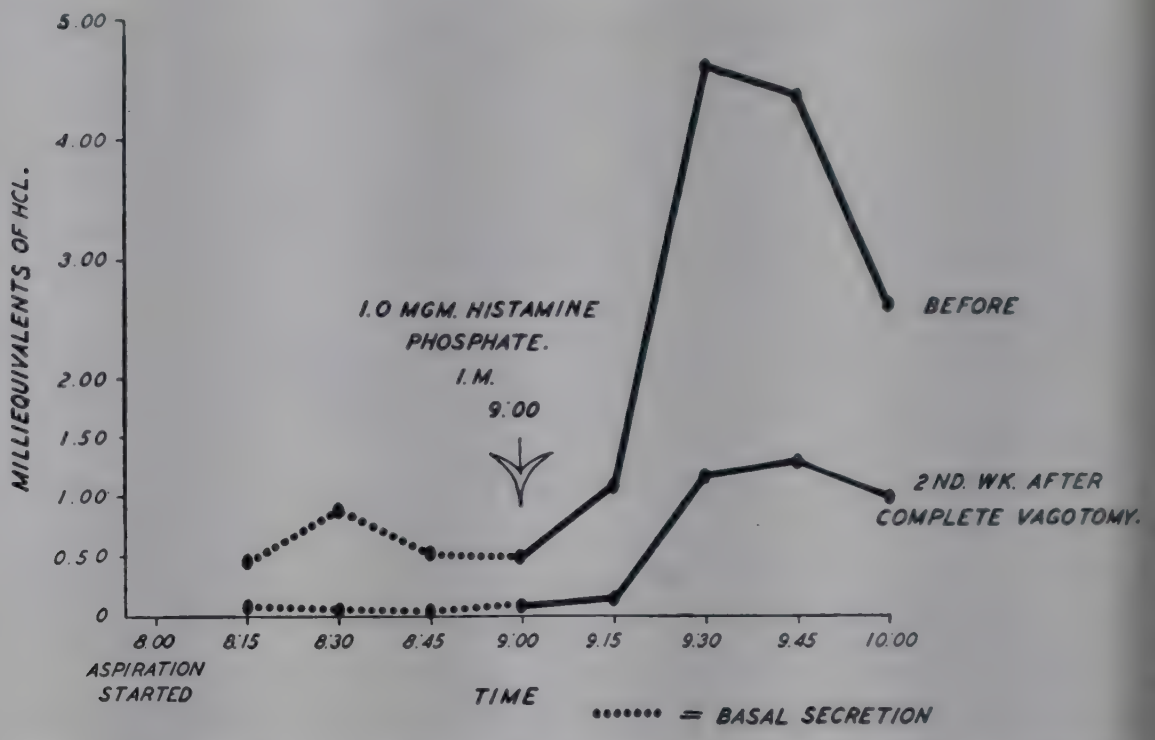


FIG. 116. The effect of histamine on gastric acidity before and after vagotomy (Stein & Meyer: *Surg., Gynec. & Obst.* **87**:188, 1948.)

that obtained in ulcer patients with caffeine alone, it was postulated tha the elevated and prolonged response to caffeine in duodenal ulcer migh indicate an abnormal release of histamine in these patients. Whethe analagous synergisms exist between caffeine and other mechanisms o gastric secretion or between the various known mechanisms of gastri secretion remains to be determined. The possibility of a caffeine-acetyl choline synergism is raised by the findings of Stein and Meyer (85 (Fig. 117).

EVALUATION OF EVIDENCE FROM VAGOTOMY. At the present time, it not possible to draw a final conclusion from the effects of vagotomy i duodenal ulcer patients as to the nature of the secretory disturbance i these patients. This reduction which follows vagotomy could be du either to the removal of excessive vagal impulses or to a decrease in th sensitivity of the parietal cells to some other stimulant which is acting i excess. Removal of normal vagal impulses decreases the responsiveness the parietal cells to other stimuli. The fact that vagotomy is followed by temporary sharp reduction in gastric secretion does not prove that th seat of the disturbance lies in the psychic or emotogenic secretion. Shou it turn out that such is actually the case, it would still remain to b determined whether the alteration is a qualitative or a quantitative on since the psychic phase, although it may be accentuated in the ulc patient (87, 88), is a normal phenomenon; an emotogenic augmentati of secretion is not limited to ulcer patients (89).

Let it be understood that we are not denying that excessive vagal activity may play an important role in the hypersecretion of duodenal ulcer. The vagus nerves exert the principle control over the secretion of pepsin; electrical stimulation of the vagus, sham feeding (which acts only through the vagus), insulin hypoglycemia, or the parenteral administration of parasympathomimetic drugs stimulate the flow of a gastric juice rich in peptic power. No strong stimulants of pepsin secretion other than the parasympathetic mechanisms are known to exist. Therefore, the evidence that the fasting gastric secretion in duodenal ulcer patients is, according to some observers, rich in peptic power (p. 702) provides circumstantial evidence that the vagus is involved.

There are two further possibilities to explain the hypersecretion. The first is *an impairment of the normal neutralizing and buffering mechanism.* As noted in Chapter 2, the regulation of the acidity of the gastric contents is controlled in part by regurgitation of duodenal secretions and by the buffering action of the nonacid secretions of the stomach. We know of no good evidence that enterogastric regurgitation is impaired in the duodenal ulcer patient, although Kearney et al. (90) stated that the flow of bile-colored juice from a tube in the second portion of the duodenum was often considerably delayed in duodenal ulcer cases. In our experience, bile is present in the gastric contents of these patients as often as in those of the

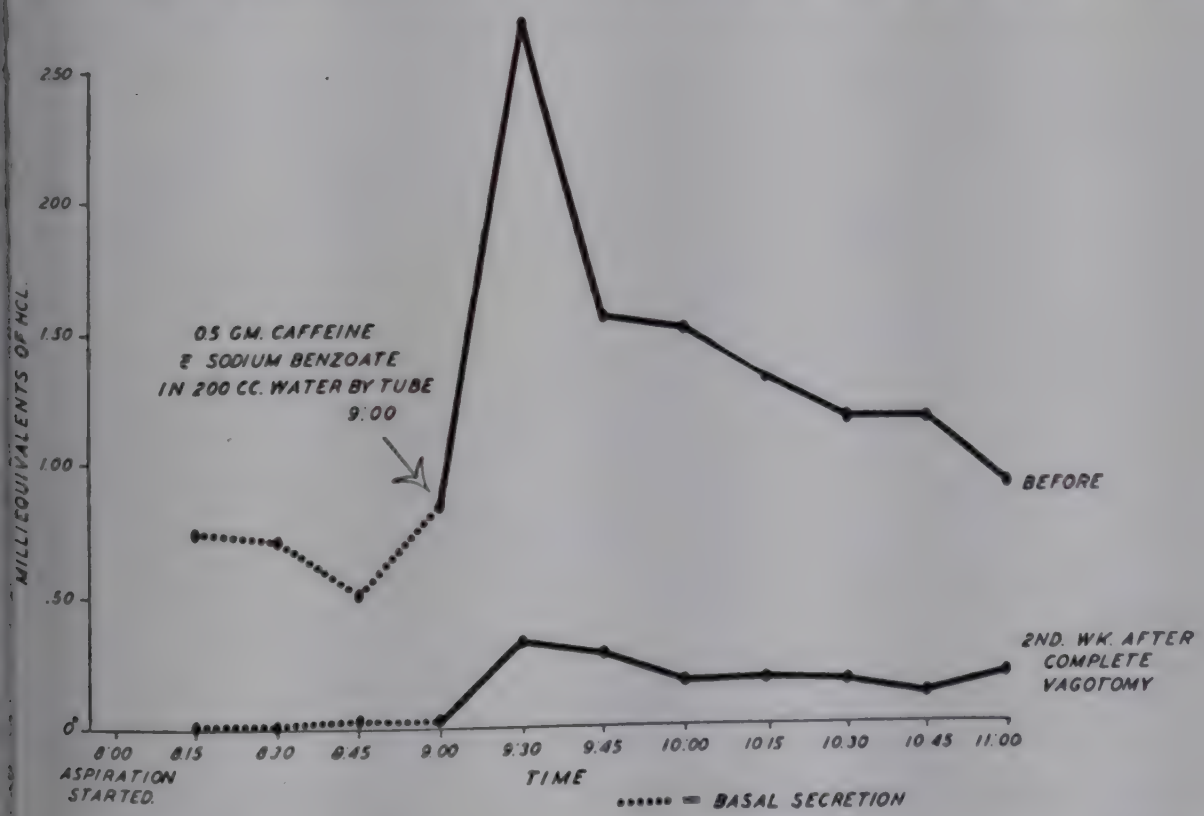


FIG. 117. The effect of caffeine on gastric acidity before and after vagotomy. (Stein & Meyer: *Surg., Gynec. & Obst.* **87**:188, 1948.)

normal. That the intragastric buffering mechanism may be deficient is suggested by those reports (56, 57) indicating that the ulcer patient secretes less mucus than does the normal person.

The second is *an impairment of the normal inhibitory mechanisms.* The principal mechanisms for the inhibition of gastric secretion are acid inhibition and inhibition by the chalone enterogastrone. Acid inhibition refers to the depression of acid secretion caused by the presence of an adequate concentration of acid in the stomach and duodenum. Whether or not acid inhibition occurs depends on the nature and potency of the secretory stimulus. No special study has ever been undertaken to determine whether acid inhibition is mediated by a nervous or humoral mechanism. The inhibition of gastric motility by acid in the duodenum is known to be a vagal reflex. Reasoning by analogy from the fact that the secretory and motility phases of depression of gastric activity by fat in the intestine are both due to a humoral mechanism, acid inhibition may be presumed to be a nervous reflex. This assumption awaits proof. Shay and his associates (91) have obtained evidence that in patients with duodenal ulcer acid inhibition from the duodenum is greatly impaired. Shay (92) believes that in the presence of an ulcer the threshold for acid inhibition is raised, so that the acid has to reach a concentration much higher than normal before the inhibitory mechanism comes into play. He states further that when the ulcer heals, the disturbance may be corrected and the gastric secretion return to normal. If we read Shay correctly, he maintains that a return of gastric secretory function to normal is a better index of healing of the ulcer than any other evidence available. This is an important concept, but it will be a difficult one either to prove or disprove if the roentgenographic findings are not to be accepted as a reliable indication of healing.

Further evidence that the processes which normally operate to depress gastric acidity are impaired in duodenal ulcer is provided by the results of the acid neutralization test of Apperly. Lately, however, this test has come to be regarded as essentially a measure of emptying.

No evidence exists that a disturbance of the enterogastrone mechanism occurs in ulcer. There is evidence indicating that there is less urogastrone in the urine of ulcer patients (p. 447).

Reaction of Duodenal Contents*

All investigators who have measured the reaction of the duodenal contents in duodenal ulcer patients are agreed that there is an impairment or an instability, or a disharmony of the duodenal neutralizing mech-

* For a review of the acidity of the duodenal contents in health and disease, Comfort (93).

ism in these patients. Einhorn, having found (94–96) that the duonal contents are ordinarily alkaline in fasting or after a bouillon test eal, observed (97) that among 19 duodenal ulcer patients the duodenal ntents after a bouillon meal were at times acid in eight, and always galine in 11. These observations were confirmed by Morton (98), who ed an Ewald type meal.

Kearney et al. studied the secretions aspirated from the second portion the duodenum in fasting and after meals. They found that in cases of odenal ulcer the average pH was lower, reached a lower level, and mained there for longer periods of time than in controls. The authors ggested three possible factors to explain these findings: (1) larger quantis of acid entering the duodenum in these patients; (2) a relative defincy of neutralizing and diluting fluid; and (3) a disturbance of the utralizing and diluting mechanism. As to the second and third points, have already shown earlier in this Chapter that there is as yet no good idence pro or con. As to the first point, all other investigators (97, 99, 0) of duodenal reaction have come to the conclusion that the *acidity* of gastric contents does not seem to be the determining factor in the dity of the duodenal contents, but they have apparently all overlooked matter of volume, and in our opinion this point raised by Kearney al. may well provide the answer. Certainly it should be investigated ore undertaking experiments seeking to elucidate more complicated chanisms.

The most extensive and painstaking study of the duodenal contents s been contributed by Berk, Rehfuss, and Thomas (24, 100–103). ing a double-lumen tube in patients with radiologic evidence of active odenal ulcer as well as in normal controls, they paid particular attenn to the duodenal *bulb* area. They observed that the neutralizing ability the duodenal bulb contents is overcome more frequently, to a greater ent, and for longer periods of time in the ulcer patient, both in fasting d after an Ewald meal. For example, in the fasting studies, the morning retion was aspirated at 10 minute intervals for 30 minutes. Of all nples taken in duodenal ulcer patients, 56 per cent were less than pH , while 26 per cent of the normals fell below this pH. After an Ewald al, free acid was present in the duodenal contents in more of the ulcer ients and in more of the samples than under fasting conditions.

The authors cited three observations tending to support the conclusion t the neutralizing mechanism in duodenal ulcer is disturbed. (1) A cted group of hypersecreting non-ulcer patients displayed, in the ond half of the observation period following an Ewald meal, a higher tric acidity and at the same time a lower duodenal acidity than did odenal ulcer patients. (2) There were sharp fluctuations in the duo-

denal acidity of duodenal ulcer patients but not in normal subjects (3) The average excess neutralizing ability of the duodenal contents o ulcer patients was greater than in normals. This paradoxical finding i attributed by the authors to a less efficient regulatory mechanism which allows wider excursions from the average than in normals.

Motility Changes in the Stomach and Duodenum

Considering how widely accepted is the belief that duodenal ulcer i characterized by hypertonicity and hypermotility of the stomach, it i remarkable that so little graphic evidence is available depicting thes changes. Information on this subject has come almost exclusively fro fluoroscopic observations.

Motility as Observed by Fluoroscopy

An increase in gastric motility is regarded as one of the seconda diagnostic signs of duodenal ulcer; e.g., Feldman (104) quotes vario observers as noting gastric hyperperistalsis in from 40 to 65 per cent cases. He states that hypertonicity, hypermotility, and rapid emptyi are a common accompaniment of the disease. Thus, according to t x-ray evidence, the stomach is abnormally active in the presence of duodenal ulcer. Since it does not occur in all, like hyperchlorhydr hypermotility is not pathognomonic or of prime etiologic significance.

Fasting Motility

Most of the kymographic studies of motility in peptic ulcer patie deal with the mechanism of pain, without mention as to whether, or what extent, the motility departs from the normal. For example, Carl (105) in referring to the medical student with a duodenal ulcer u whom he was performing balloon-kymographic experiments, sta "Between relapses his motility was that of a normal person." Nothing said concerning the motility during the relapse.

Onodera et al. (106), although using a technically faulty meth concluded that in the absence of obstruction the elevated tonus increased length of contraction periods as recorded by the gastrogra method are more accurately diagnostic than the x-ray. Anderson (107) the basis of kymographic studies in 10 duodenal ulcer patients, concl that in these patients the gastric tone is increased and that the contrac are stronger and more frequent than in the healthy stomach, tend to and often end in a state of tetanus. A most significant observation desc by Anderson was the "water reversal phenomenon." He found tha introduction of four ounces of cold water into the stomach of a duo

ılcer patient does not inhibit peristalsis as it does in the normal person. Pollard et al. (22) have made an intensive study of the fasting motility in duodenal ulcer patients. They find in these individuals all gradations of gastric activity ranging from a single brief period of "hunger contraction" in a three hour observation period to an almost continuous motility. As far as we are aware, no one has presented kymographic evidence comparing the fasting motility while the ulcer is active and when it is healed. Furthermore, a comparison of the fasting duodenal motility in normals and in ulcer patients has not, to our knowledge, been the subject of a special kymographic study. The spasm of a duodenal cap which is the site of an ılcer is, of course, a common roentgenographic observation.

Observations in Animals

Experimentally, it has been reported (108) that duodenal or antral ılcers produced in dogs by submucosal injection of silver nitrate caused an increase of the fasting gastric motility in three of four animals. In our experience (109), gastric emptying was delayed by the presence of a silver nitrate ulcer in the duodenum or near the pyloric outlet and gastric motility was increased. Because of the acute nature of ulcers resulting from silver nitrate and their rapid healing, these experiments are perhaps not so satisfactory as those of Wolfer (45). He produced chronic ulcers by x-ray just proximal to the pyloric sphincter and reported a delay in gastric emptying.

Mechanism of Hypermotility in Duodenal Ulcer

Impairment of a Normal Inhibitory Mechanism

According to Shay (92):

> With the development of the ulcerative process . . . the duodenal mechanism concerned with gastric motor delay becomes impaired. Stimuli reaching the duodenum which would activate this mechanism fail to do so as readily as under normal conditions. The normal brake not acting efficiently, gastric peristalsis, tonus and gastric evacuation are exaggerated, resulting in the hyperperistalsis, hypertonicity and rapid gastric evacuation seen so frequently in uncomplicated duodenal ulcer.

It is Shay's further contention that since the above changes are due to the ulcer and the associated duodenitis, the motor functions of the stomach will return to normal after the ulcer has healed. The experimental evidence supports Shay's hypothesis to the extent that an ulcer in or near the duodenum *can* bring about an augmentation of gastric motility. When the experimental ulcer heals, the stomach once more functions as it did before the ulcer was present, i.e., normally. If the healing of the clinical ulcer is followed by a resumption of the kind of gastric activity

which was present before the ulcer developed, it may or may not be normal.

Shay has not yet ascertained how the inhibitory mechanism operates; consequently, it is not possible to speculate on how it is impaired. Of interest and practical importance is his observation that in some cases where the application of acid to the duodenal mucosa does not inhibit gastric activity, the introduction of fat will bring about some inhibition. He interprets this as indicating that the regulating function is impaired, not abolished. We suggest as an alternative possibility that two different mechanisms are concerned, a nervous mechanism for inhibition by acid and a humoral mechanism for inhibition by fat, and that the one may be lost while the other remains.

In duodenal ulcer, an initial delay in gastric evacuation need not be accompanied by a terminal delay. In the absence of an organic stenosis of the pylorus, a hypertonic pyloric sphincter could cause initial delay until the pressure in the stomach became adequate to overcome it. Then, large quantities of chyme could be ejected into the duodenum with each opening of the pyloric sphincter, or a "gastric hypertension" could predispose to a more rapid evacuation than normal even in the presence of some hypertonicity of the pyloric sphincter.

Another factor concerned in the rate of evacuation is the enterogastric reflex. This reflex is initiated on distension of the duodenum and both the afferent and efferent limbs of the reflex are in the vagi. Hence, with the vagi intact, a rapidly evacuating duodenum will predispose to rapid evacuation of the stomach.

Vagal Hypertonus

There is no question concerning the characteristics of the gastric juice which is secreted in response to vagal stimulation but it is not clear whether vagally mediated gastric motility has a characteristic configuration. From our studies (109), we gained the impression that Type I contractions are the only type occurring in dogs after supradiaphragmatic section of the vagi with or without subdiaphragmatic section of the splanchnic nerves. They occurred after section of the vagi alone and it has been taught by us that contractions on tone are dependent on the vagi. In our experience, after complete vagotomy the gastric hunger contractions all rise from the same base line of pressure, as fasting continues the contractions increase in amplitude, and fasting as long as 48 hours does not result in any evidence of Type II and III contractions or contractions on marked tone. Vagotomy, however, did not abolish the delayed evacuation due to an acute ulcer of the duodenum or pyloric antrum.

In dogs with the vagi sectioned, Type II contractions eventu-

ppear, according to Carlson. On the other hand, these experiments ere performed before the hypoglycemia test for complete vagotomy was orked out and, therefore, the matter remains to be clarified. If a particur motility pattern could be identified as representing vagal overactivity, might contribute materially toward an understanding of the hyperotility in duodenal ulcer.

All observers are agreed that division of the vagus fibers generally olishes the fasting motility in duodenal ulcer patients for a period of me months. Whether any of these patients ever recover a motility ttern similar to their preoperative one remains to be seen. If they do not, e assumptions which may be made are (a) that the hypermotility was ue to excessive vagal tone, or (b) that the vagus was merely a link by hich abnormal or excessive impulses originating elsewhere, e.g., the ıtral mucosa, were transmitted to the musculature of the stomach. If the eoperative hypermotility is eventually recovered, a primary vagal rtonus as the principal cause is ruled out and the implication would that vagotomy does not eliminate the only pathway by which the sturbing influence is conveyed to the stomach.

Comment

It appears probable that in those duodenal ulcer patients who manifest hypertonicity and hypermotility of the stomach, with or without a layed emptying, the explanation for the disturbed function is not to be ınd in a single mechanism. In some instances, a hyperactivity of the mach is present before the ulcer develops; in such cases, the motility sturbance may be intensified, although it certainly is not caused, by the cer. Whatever the nature of the motility change, it apparently does not erfere with nutrition in the *uncomplicated case*. That is, in so far as the otor disturbance affects the digestion of a meal, the results are not leterious from a symptomatic point of view, inasmuch as the patient ls better when he has food in his stomach. As was pointed out in the cussion of secretion, the main problem is: What happens when the mach is empty?

In our opinion, kymographic observations with a balloon in the mach provide an indispensible source of information regarding the ting motility and more studies of this type are indicated in duodenal er. The objection that the presence of a balloon in itself provides a mulus for gastric activity is not valid because the fasting stomach will erate a balloon for hours without showing any contractions or tonus anges. Moreover, the balloon does not have to be so big as to simulate arge bolus; e.g., the contractions recorded in Figs. 106, 107, and 108 674) were registered with 10 cc. of air in a balloon which required

40 cc. to put its walls on the stretch. Such an arrangement provides har any more stimulation to the stomach walls than does the stomach t itself.

The great advantage of the balloon procedure is that it provide convenient opportunity to investigate the motility disturbance by the of drugs; furthermore, it may aid in clarifying the pharmacologic ac of drugs. For example, the question arises: What is the effect of atro on the gastric motility when it begins to appear following complete va omy in man? This is much more easily, and above all more accurat determined by kymographic than by radiographic observations.

Pathologic Physiology of Gastric Ulcer

Gastric Secretion

There is no typical secretory change in gastric ulcer. As indicate p. 692, the basal secretion, the nocturnal secretion, and the respon stimuli such as histamine and caffeine show the same wide range of v as is seen in normals of corresponding age. The average values fo basal secretion (52) and the nocturnal secretion (37) do not exceed of the normal (Table 116) and, if anything, tend to be less thar

Table 116

Average Values of Basal Secretion and 12 Hour Nocturnal Gastric Secr in Normal Males and in Patients with Gastric Ulcer

	*Basal**			*Nocturnal†*		
	Average Vol. per 20 Minutes Cc.	*Average Free Acidity M. Eq./L.*	*Average Pepsin Units*	*Average 12 Hour Volume Cc.*	*Average Acidity M. Eq./L*	*A. O*
Normal.....	12.6	57.8	40.4	643	30	
Gastric Ulcer.....	17.1	41.0	38.8	623	12	

* Ihre (29).

† Levin et al. (86).

normal as to concentration of acid. We (11) found that the curve average gastric secretory response to caffeine in gastric ulcer patien midway between the normal and the duodenal ulcer curve.

Gastric Motility

There is usually *no* augmentation of motility in gastric ulcer matter of fact, according to Feldman (104), there is generally a hyp

nd an inhibition of peristalsis. Other changes observable at fluoroscopy consist of local spasm in relation to the ulcer and occasionally a retention due to pylorospasm. Brauch (110), on the basis of kymographic studies in 64 patients, concluded that the ulcer stomach manifested a "poikilo-peristalsis." He expressed the opinion that if one could feel the gastric movements as one feels the pulse or hears the heartbeat, the symptom of "arrhythmia gastrica" would long ago have been as well recognized in gastroenterology clinics as are the arrhythmias in cardiac pathology. His kymographic method was not satisfactory, however, and it is not possible to obtain from his curves a satisfactory idea of the changes he claims to have found. In fact, we are not aware of any good study of the gastric motility in a large series of gastric ulcer patients. Ulcers in the prepyloric region and in the pyloric canal tend to give secretory and symptom patterns similar to those encountered in duodenal ulcer.

Gastrojejunal Ulcer

Gastric Acidity in Gastroenterostomy

It has been clearly demonstrated that the secretion of acid by the stomach is essential in the cause of postoperative jejunal ulcer in the dog, in which species this ulcer occurs with the same frequency as it does in man (10 to 25 per cent). This well established fact indicates that the acid factor should be of prime etiologic importance in the genesis of gastrojejunal ulcer in man. This would indicate that it should be significant to inquire about the changes in gastric acidity after gastrojejunostomy.

In 1933, Vanzant et al. (7) studied by the Ewald test-meal the acidity of patients who after gastroenterostomy returned with a jejunal ulcer. It was found that the acidity of those with jejunal ulcer was not higher than those similarly operated on who were symptom-free for two years or longer. The mean acidity of the patients with jejunal ulcer was 12.5 units higher than the normal group, which is the same extent to which the duodenal ulcer group exceeded the normal group. Thus, nothing was found which would help recognize those duodenal ulcer patients who would develop jejunal ulcer after gastroenterostomy.

Much of the literature on this topic was reviewed by Holman and Sandusky (111) in 1938. If the results of one investigator (Sherren), who reported an extraordinarily high percentage of anacidity following gastroenterostomy, indicating that the tube had passed into the jejunum, are omitted, the following are the average changes observed after the operation in 388 cases: 20 per cent showed hyperacidity, 26 per cent normoacidity, 28 per cent subnormal acidity, and 25 per cent anacidity. It is exceedingly doubtful whether these changes are statistically signifi-

cant, even if it is granted that the position of the tube was in the stoma or not distal to the stoma. Holman and Sandusky found that no signific change occurred in 92 per cent of 75 patients on whom they had p formed a gastrojejunostomy and a histamine test before and after operation. This work conforms with the observations of several ot investigators as well as those of Vanzant et al.

COMMENT. It seems clear that the level of acidity in pre- and po operative gastroenterostomy has no prognostic value. These observati have etiologic significance in that, like duodenal and gastric ulcer hyperchlorhydria or hypersecretion is not requisite for the format of an anastomotic ulcer. It should be recalled in this connection t the M-W dog tends, like the duodenal ulcer patient, to secrete more a but jejunal ulcer may occur in approximately 25 per cent of animals wi normal secretion. This again indicates that a second factor, probabl individual susceptibility, other than acid is also concerned in the deve ment of anastomotic ulcer.

Peptic Ulcer and Anacidity or Achlorhydria

It is clear from the evidence cited before that duodenal ulcer occur in the presence of a normal gastric secretory response and th gastric ulcer may occur in the presence of a normal or subnormal ga secretory response. The question arises as to whether a peptic ulcer occur in the presence of achlorhydria, as an oral apthous ulcer does.

Many cases of peptic ulcer have been reported in the presenc achlorhydria as examined particularly by the Ewald test-meal or modification of it. Palmer, in 1929 (112) and again in 1940 (113), revi the literature claiming that a peptic ulcer was found in the presen achlorhydria. In both instances, he concluded that chronic peptic has not been observed in a patient with a histamine-proven anac He (113) states that he has gastric acidity records on 2200 patients peptic ulcer and none have had achlorhydria. Bockus (48) agrees Palmer. Both point out that Kahn (114) autopsied 840 cases of pern anemia and Washburn and Rosendaal (115) saw 906 cases of pern anemia without seeing a single case of acute or chronic ulcer of the sto or duodenum.

We have checked the literature since 1940 to find if there wer reports of ulcer patients who have been persistently anacid on the ap tion of three histamine tests several days apart. Odin (116) repo number of cases of duodenal and gastric ulcer in the presence of ach dria, some of which did not respond to one histamine test. Lasher has reported anacidity in four elderly patients with proven benign of the stomach, using one alcohol or histamine test. We have recent

patient with a gastric ulcer on the lesser curvature after a gastroenterostomy for a duodenal ulcer. The ulcer was diagnosed as benign by gastroscopy and healed in three weeks according to x-ray and gastroscopic examinations. The patient was achlorhydric on two double dose tests, but secreted free acid on a third test within 10 days in response to 0.1 mg. of histamine dihydrochloride per 10 kg. body weight. Some claim that Palmer demands too much evidence to prove that a gastric or duodenal ulcer will occur in the presence of achlorhydria. This is not correct because it is obviously important to decide whether a peptic ulcer is a peptic ulcer or whether it will occur in the absence of acid, since acid is required for the action of pepsin.

Anyone who has done repeated gastric secretory tests on the same individuals knows that the response varies considerably, regardless of whether the stimulus is meat broth, a carbohydrate Ewald meal, caffeine, alcohol, or histamine. Anacidity is recognized as occurring in syphilitic, tuberculous, and carcinomatous ulcers. Therefore, we agree with Palmer when he insists on several histamine tests before the diagnosis of achlorhydria is made in the presence of gastric or duodenal ulcer, and on careful examination of the patient before the diagnosis of peptic ulcer is made in the presence of achlorhydria.

Two questions are involved in the consideration of this topic. One pertains to whether acid is essential for the genesis, course, and pain of gastric and duodenal ulcer; the other to whether an excessive secretion of acid is essential for the genesis of peptic ulcer.

It seems quite evident that an excessive secretion of acid is not the only factor concerned in the genesis of peptic ulcer. On the contrary, there is good evidence showing that a chronic ulcer of the stomach or duodenum will occur in the persistent absence of acid from the gastric contents, in the absence of acute gastritis, syphilis, tuberculosis, or cancer of the stomach.

It is important for anyone who finds a crater in the stomach or duodenum with apparent achlorhydria, first, to ascertain whether it is a nonspecific ulcer and, second, to determine over a period of several weeks and months by means of histamine whether a persistent achlorhydria exists in the patient. This will be necessary to prove that peptic ulcer is not in any way related to acid.

Seasonal Occurrence of Peptic Ulcer

The tendency for ulcer symptoms to develop or recur at certain seasons or months of the year is rather characteristic of peptic ulcer (p. 549, 590, and 626). We believe that there is insufficient evidence to demonstrate a difference in duodenal and gastric ulcer in this respect.

The reasons for the seasonal pattern are not clear. A study o secretion and other physiologic functions, such as growth and re the study made by Riggs et al. (118) on certain changes in the b cardiovascular systems with seasons will have to be conducted. I be recognized that all considerations of the question are at speculative (119, 120) and that in order to show a significant d between different months a large series of patients is required the factor or factors concerned are not very potent or obvious.

Upper Respiratory Infection

Moynihan (121) thought that attacks of duodenal ulcer mainly during the winter season (December, January, Febru that these attacks were precipitated by upper respiratory i Moynihan was greatly impressed with the relationship betwee cold" and the onset or recurrence of ulcer symptoms. For exa

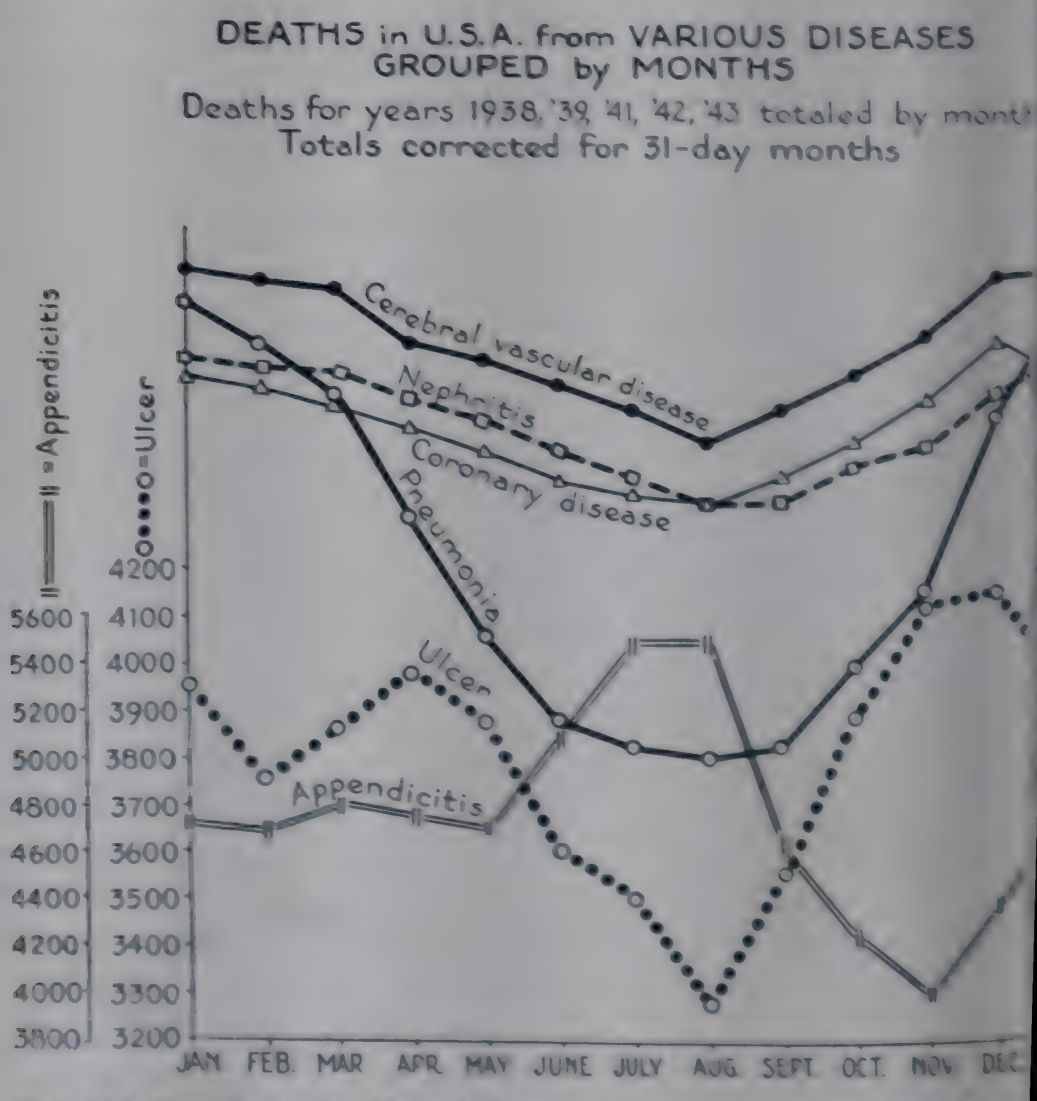


Fig. 116. Deaths in the United States of America from various disea by months.

hat a chill may bring on an attack in a few minutes and the symp- may continue for months. Einhorn (122) also regarded upper tory infection as the most important precipitating factor; however, xperience the disease appeared more often during the spring and n during the winter. He suggested that the onset of the rainy in the fall and the temperature instability in the spring were ible for the "colds" and secondarily for the ulcers. As indicated re (p. 633), Emery and Monroe (123) found that only 13 per cent patients ascribed the onset or recurrence of their attack to an respiratory infection.

order to ascertain if any correlation existed between the seasonal ty of peptic ulcer and various diseases, the graphs in Fig. 118 were The peptic ulcer curve is low in the summer and high in the late ovember and December), unlike appendicitis and like vascular nephritis, and pneumonia.

Rough and Irritating Foods

gmann (124) was among the first to call attention to the high nce rate in the spring and fall; in his clinic the peak incidence was l in the spring. In his opinion, the most plausible reason was the ption of vegetables and salads in the spring and fruits in the fall. d, in support of this view, the occurrence of duodenal ulcer in at the time of weaning from milk (see p. 49). Sällström's (119) of the dietary habits in Sweden indicated that the consumption of roots, fruits, and berries is lowest during the period of lowest ulcer cy (May and June) and highest at the time of maximum ulcer cy (August and September). However, the differences in the level e of these foods were not striking.

Endocrine Activity

nheim (125) proposed the theory that in the spring and fall there flux of blood to the sex organs in association with the estrus cycle a result the superficially healed peptic ulcer, deprived of adequate ion, breaks down. Alkan (126) disagrees; he states that (1) there trus cycle in man comparable to that in lower animals and (2) stomach symptoms" occur after the menopause. But Hutter (120) idence of increased sexual drive in man in the late spring, though nuch in the fall, the season which Cohnheim thought was attended strongest estrus phase. Moreover, as Hutter pointed out, the well amelioration of ulcer symptoms by pregnancy indicates that some ion exists between the sex organs and peptic ulcer. The possible ships have already been discussed (Chapter 13).

Other Causes

Ellinger (127) outlines a hypothetic basis for spring and fa
rences as a result of the following observations and reasoni
ultraviolet light sensitivity of "vegetatively stigmatized" indivi
found to be greater than that of nonstigmatized individuals of co
complexion. Greater light sensitivity means more erythema o
from a given degree of exposure, which means the liberation
histamine-like substance from the skin, resulting in the stimulation
secretion. Ulcer-bearers are, according to Bergmann, "vegetatively
tized"; consequently, ulcer patients are probably more light-sensi
normals and when more ultraviolet rays reach the earth in th
these patients get recurrences. Although there is even more su
the summer, the disease improves because the heat counteracts
secretion; a relapse occurs in the fall because there is still plen
shine while the temperature is lower.

Gebhardt and Richter (128) explain the summer remissio
grounds that more "normacid curves" are found among ulce
during the summer. This is plausible enough; however, no
given.

The decrease in the incidence of ulcer during the summer mo
be due to summer vacations or to the decrease in the drive to a
which is believed to be incident to warm weather.

In this connection, it is also worthy of mention that a cha
yield of gastric mucin from the gastric mucosa of the hog occ
the fall and spring months. During the winter, the yield is grea
mucus thicker. The meaning of this is not clear.

Mechanism of Pain in Peptic Ulcer

In 1884, Talma (129) observed that the introduction of di
chloric acid into the stomach in two cases of dyspepsia resulte
He postulated that pain in gastric disorders is due to a hyper
the gastric mucosa to acid. In 1888, Suyling (130), in Tal
reported that he had demonstrated this phenomenon in a pa
nosed as having a gastric ulcer. A few years later, Lowenthal
lenged the concept of Talma and Suyling. He considered it i
speak of hyperesthesia to acid on the basis of observations
stomachs, just as one does not speak of hyperesthesia of the sk
a skin ulcer becomes painful on application of a chemical ag
normal skin is indifferent. Lowenthal's experience was that
experienced by the normal individual when hydrochloric a
was introduced, even in higher than physiologic concentrati

ere the matter apparently rested until 1908, when Bonninger (132) ed that the introduction of 100 to 200 cc. of 0.1 N HCl into the ch constituted a simple, reliable diagnostic and prognostic test tic ulcer. Given a patient in whom pain is a part of the symptom e, if the introduction of acid did not result in pain even after chang- e patient's position so as to allow the acid to come in contact with rts of the stomach, then in the author's experience it could be stated certainly that there was no ulcer. He observed further that as the healed, the intensity of the pain response decreased progressively disappeared. Schule (133) rediscovered this test in 1926 and added servation that the pain could be terminated by the introduction olution of sodium bicarbonate. At the same time, Palmer began his gations on the use of the "acid test" for peptic ulcer (134) and on le of acid in the mechanism of ulcer pain.

e are not concerned here with the merits of the "acid test" in the osis of peptic ulcer. The foregoing outline has been given only to the development of the concept that the pain of peptic ulcer is acid. This was apparently the generally accepted viewpoint until when a series of experiments performed at the University of Chicago ced the theory that the pain is due to contractions of the stomach. ypothesis was apparently accepted and remained for the most part llenged until Palmer started his series of experiments on the relation er pain to the motor and secretory activity of the stomach. His timulated a great deal of investigation into the problem, with the that there has arisen a considerable amount of disagreement on causes the pain in peptic ulcer. Rather than analyze the arguments d against the respective theories, we wish to outline briefly the ce which has been obtained according to the method by which the m has been attacked. By reviewing the subject from this standpoint, pe to be able to indicate how much is established as dependable ation. From this we hope to make it apparent what kind of evidence ed to clarify the matter further.

Evidence from Introduction of Acid into the Stomach

lmer has demonstrated repeatedly (112, 134, 135) that the intro- n into the stomach of 200 cc. of 0.5 per cent HCl will produce the distress of an ulcer patient and will produce no distress in a l individual. Other chemical irritants such as sulfuric acid, acetic nd sodium hydroxide were shown to have the same effect. The period (several minutes) before onset of the pain depends on the quired for the acid to cause a contraction of the musculature about he region of the ulcer, or the time required for the nerve ending

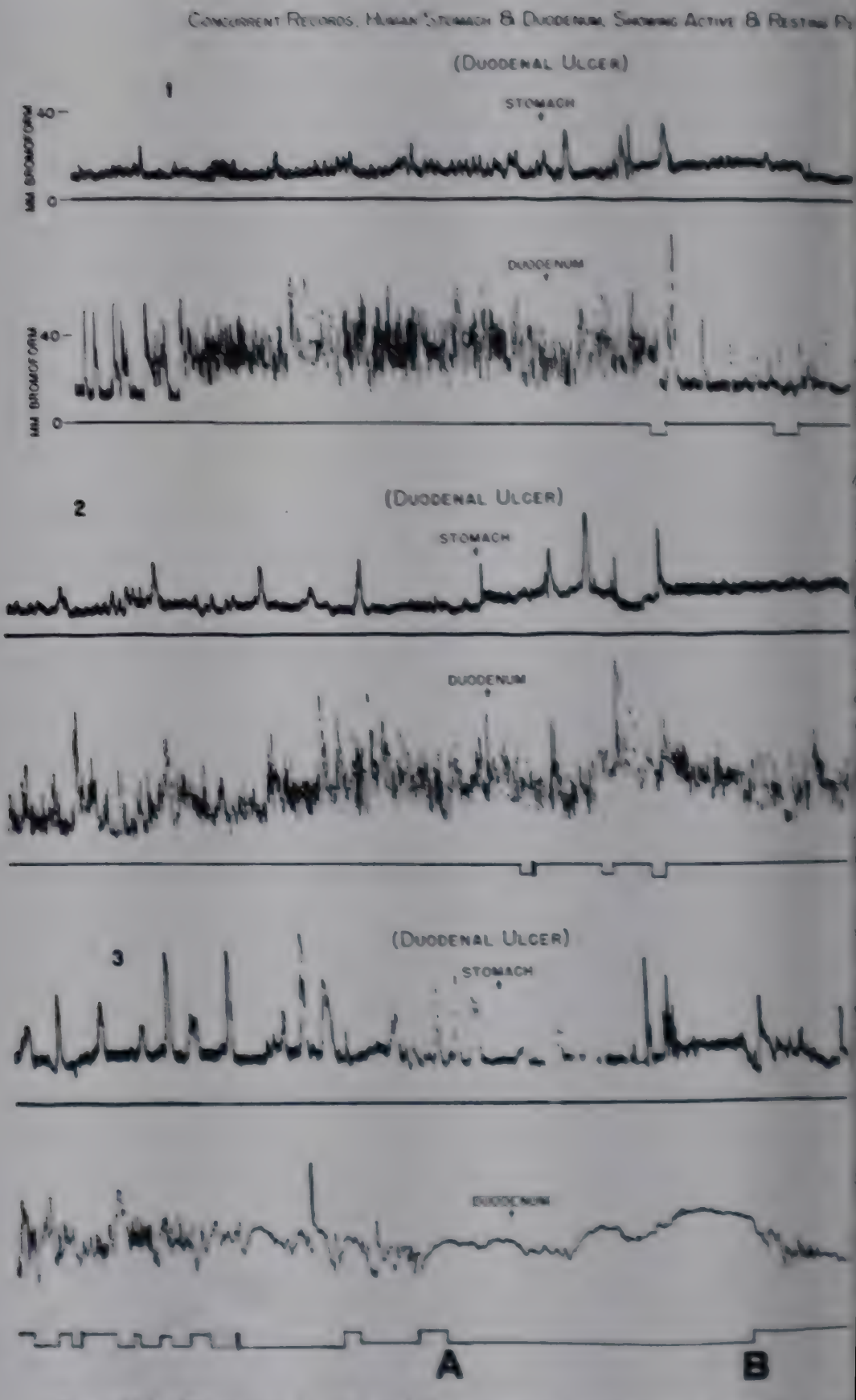


FIG. 119. Tracings 1, 2, and 3 represent continuous, synchronous duodenal motility phases during a 2½ hour study. Note signaling of sleep recorded by the patient at the bottom of the tracing. These increase in

ied" in the base of the lesion to be stimulated sufficiently to convey ensation of pain, and, in the case of duodenal ulcer, the time required he acid to empty from the stomach into the duodenum. A healed is insensitive. Moreover, not all ulcers will respond with pain upon ntroduction of acid. Finally, the distress provoked by the acid is inated in three to 10 minutes by withdrawal of the acid or the intro- on of alkali. These observations prove that acid is an adequate ulus for the initiation of pain in peptic ulcer and that acid may be the timulus in certain cases.

lardy (136) was able to confirm Palmer in part but concluded that plays no essential part in ordinary pain production. His objections essentially these three: (1) distress could not be produced in *all* of ulcer; (2) introduction of acid sometimes caused pain (not ibed) in non-ulcer cases; and (3) the pain did not appear immediately introduction of the acid. None of Hardy's observations justify his usion that acid plays no essential role in the pain of ulcer.

Evidence from Observations on Motility Alone

YMOGRAPHIC STUDIES. Several observers (137–139) have reported he pain of peptic ulcer coincides with the "hunger contractions" of tomach, as recorded by the balloon-kymograph method. These ers concluded that the pain is due to gastric muscular activity. uch as no efforts were made to ascertain whether or not acid was t at the time of the pain, it is obvious that these observers did not vidence to support their belief that acid plays *no* role. For example ns (140), using the same technique, encountered pain in the e of gastric contractions and contractions in the absence of pain.

a result of observations on the motor activity of the small intestine g hunger, we (141) suggested that the contractions of the duodenum g hunger and the latter part of digestion could be a partial explana- r the intermittent pain associated with duodenal ulcer. Subsequently, son and Sandweiss (142) conducted studies of the gastric and duo- motility in four duodenal ulcer patients and found that ulcer distress ot occur when the duodenum was quiescent. The patients experi-

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ration and occur only when the duodenum is in an active phase, the stomach ither active or quiescent. Note also signaling of ulcer pain represented by tracing 3, which lasted for about 18 minutes. The patient was extremely fortable, complaining bitterly of epigastric pain explained by him as of ulcer. The duodenum during that period exhibited a marked increase s and passed into a state of incomplete tetanus which continued until the ased. With the cessation of pain, the duodenum relaxed and continued its . (Courtesy, Patterson & Sandweiss: *Am. J. Digest. Dis.*, **9**:375, 1944.)

enced pain when the stomach and duodenum both were exhibi motility or when the duodenum alone exhibited motility (Fig. 1 Acidity was not investigated and the authors concluded merely duodenal activity may be one of the factors in ulcer distress.

Roentgenographic Studies. It is a common observation at fluoroscopic screen that a duodenal ulcer patient will complain of ten ness when pressure is made on the epigastrium overlying the duod bulb. Pain occurring in ulcer patients under fluoroscopic examina may or may not coincide with motility (143, 144). The factors which be responsible for these discrepancies are that the pain threshold vary from time to time and that the contractions may not be "on suffi tone" or occur with sufficient local tension to reach the threshold of pain nerves.

Evidence from Observations on Motility in Relation to Gastric Acidity

Kymographic Studies. Carlson's (105) conclusions regarding the o of the epigastric pains in gastric and duodenal ulcer were appar drawn from observations on one patient with a duodenal ulcer. In case, pain occurred during the height of gastric contractions, regar of the acidity. However, there was acid present; moreover, it is not that the acid concentration was determined at the time the pain occu Hardt (145) made a statement which, if supported by evidence, wou very important, viz., that "there may be intense intermittent synchronous with the contractions with no free acid in the stomach. claimed further that the pain was temporarily relieved in one instan the introduction of 0.3 per cent HCl solution with slight diminuti the contractions; the tracing illustrating this phenomenon shows, o contrary, that the "pain signals" were frequent after the HCl was duced, while the motility decreased from high waves to tonus rhythm

Ortmayer (146) administered sodium bicarbonate and ca carbonate to neutralize gastric acidity in ulcer patients during p when kymographic tracings showed contractions of the stoma association with pain. In 23 such episodes, the pain was invariably pletely relieved by the neutralizer; yet in nine instances there w change in peristalsis and in 10 the motility was increased to a v degree. In only three cases did the motor activity of the stomach de with the relief of pain, and in one there was a temporary decrease, fol by an increase beyond the prealkali period. Christensen (147) al served relief of pain by alkali in spite of persisting contractions, b attributed this to "a strong anesthetizing effect on the mucous mem by the liberated carbon dioxide.

Palmer (148, 149) demonstrated, by simultaneous motility and acidity udies, that the continuous aspiration of gastric juice relieved ulcer pain ven when contractions were present, and that the reintroduction of this iice into the stomach caused severe pain even though no contractions upervened. Administration of calcium carbonate also brought relief, lthough motor activity of the stomach was present. Smith et al. (150) ould not confirm these observations. In their experience, ulcer pain lways coincided with an increase in gastric tonus and the passage of a eristaltic wave. That acidity was not the primary factor was illustrated y the fact that pain occurred during contractions at a time when the ontents of the stomach had been rendered highly alkaline by the ad- inistration of 2 per cent NaOH. The authors apparently did not con- der that strong alkali might be as adequate a chemical irritant as rong acid.

Meyer et al. (151) found that some patients who responded to the cid test" had no pain in relation to motility, whereas some had no action to the "acid test" but had pains during periods of gastric con- action. However, determinations of acidity during the kymographic cordings were not made. According to Dimitriu et al. (152), 50 per cent their cases manifested hypochlorhydria and 10 per cent achlorhydria uring periods of pain associated with motility. Just what they mean by is is not clear, since in one of their examples the HCl concentrations uring pain are noted as 0.4 per cent and 0.7 per cent respectively.

Fluoroscopic Studies. In the experience of Palmer (148, 149), pain duced by the administration of an acidified barium meal was not accom- nied by fluoroscopic signs of elevated intragastric tension. Cobet and utzeit (153), using the same method, observed neither pain nor any fference in the x-ray appearance from the regular barium meal taken ven days earlier.

In duodenal ulcer patients suffering from pain at the time of examina- n, Wilson (154) reported that filling of the duodenal cap with gastric ntents by manual pressure on the abdomen was followed by relief of in in 13 of 16 cases, in 11 of which the gastric contents were strongly id. He concluded that pain was not due to acidity but to sustained ntraction of the cap.

Evidence from Effect of Atropine

According to the evidence submitted by Palmer and Heinz (149), opine does not prevent the appearance of pain when acid is introduced o the stomach, even though no motility ensues. This is shown in . 120. Smith et al. (150) found that the pain is abolished along with appearance of peristaltic waves, in spite of the presence of a high free

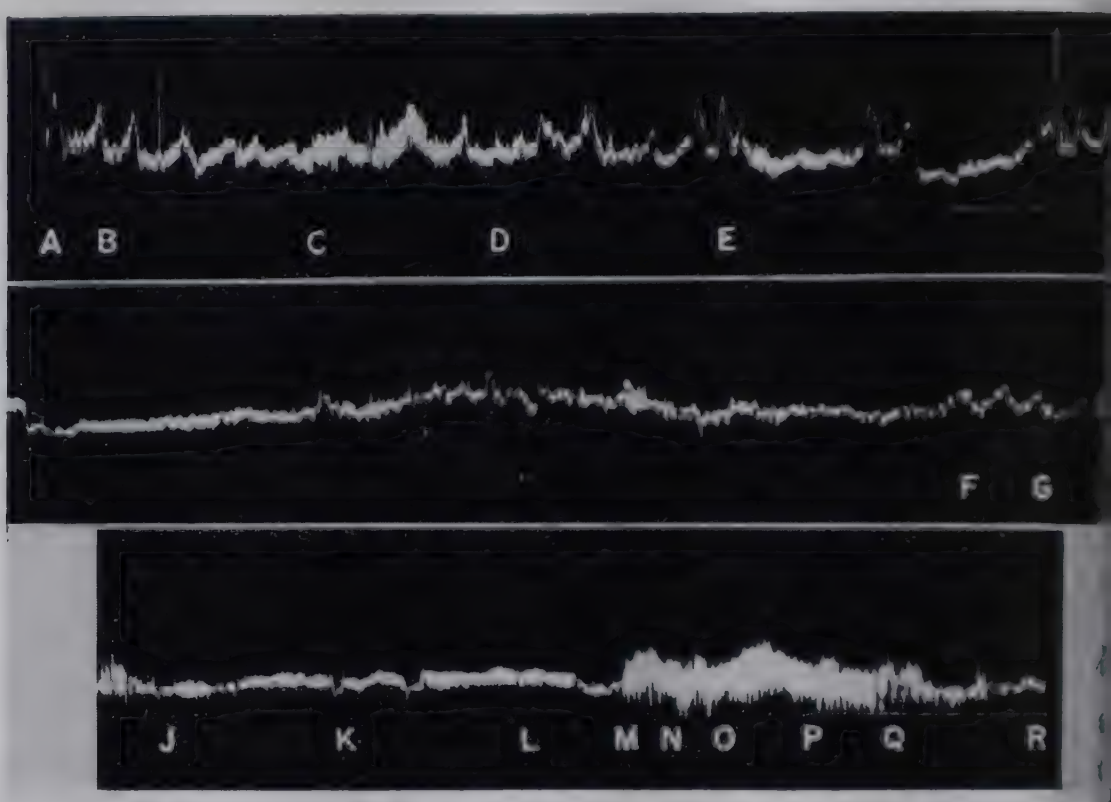


FIG. 120. *A*. (11:15 A.M.) Noted spontaneous distress. Stomach aspirated, yie
a free acidity of 45.
B. (11:20 A.M.) Distress disappeared.
C. (11:30 A.M.) Distress recurred; 20 cc. of gastric content, free a
60, obtained.
D. (11:36 A.M.) Pain half gone.
E. (11:43 A.M.) Pain completely gone.
F. (12:30 P.M.) Continuous aspiration from *E* to *F* yielded 45
gastric juice, free acidity 64, and kept the patien
from distress.
G. (12:32 P.M.) 1 mg. of atropine sulfate was given intravenousl
at the same time 35 cc. of gastric juice with
acidity of 64 was reintroduced.
H. (12:35 P.M.) Severe pain.
J. (12:42 P.M.) Pain beginning to subside.
K. (12:50 P.M.) Pain gone.
L. (12:55 P.M.) 10 cc. of gastric juice, free acidity 60, aspirated;
of 0.5 per cent solution of hydrochloric acid introd
M. (12:58 P.M.) Agonizing pain.
N. (1:00 P.M.) Unbearable pain.
O. (1:02 P.M.) 90 cc. gastric juice, free acidity 95, aspirated.
P. (1:05 P.M.) 4 Gm. calcium carbonate given.
Q. (1:08 P.M.) Pain subsiding.
R. (1:12 P.M.) Pain gone. No free acid in gastric contents.

In this experiment, atropine sulfate failed to prevent the production
by the physiologic medium of the patient's own gastric juice or by the a
stimulus of a 0.5 per cent solution of hydrochloric acid. (Courtesy, Pa
Heinz: *Arch. Int. Med.*, **53**:269, 1934.)

idity. These discrepancies may be explained by the dose of atropine ed, the extent of the tone on which the peristalsis occurs, and the esence or absence of a local spasm which will or will not respond to ropine. The observations show that the response to acid or atropine is riable. Palmer believes that, in those instances in which atropine olishes pain during an acid test in a patient with duodenal ulcer, the lief is due to the inhibition of gastric emptying with consequent failure the acid to reach the duodenum.

Evidence from Direct Observation

This type of evidence has been obtained during operations on peptic cer patients under local anesthesia. Westphal and Katsch (155) reported at electrical stimulation of the antrum resulted in an intense spasm companied by pain typical of the patient's ulcer pain. No direct anipulations of the ulcer were reported. Dragstedt and Palmer (156) ted ulcer distress in connection with three phenomena, (1) mechanical mulation of the ulcer by pressure between the fingers, massage, or ction, (2) chemical irritation of the ulcer by exposing the lesion to per cent HCl, and (3) local spasm of the duodenum just distal to the er. Meyer et al. (151) could not produce pain in any of four cases in ich HCl in concentrations up to 5 per cent was applied directly to ulcer.

Discrepancies of this sort may be explained by differences in the pain eshold in the tissues about the ulcer, such as might be due to the degree inflammation and also to the extent of the disturbance of the mecha- m for the appreciation of visceral pain in consequence of the effect the local anesthesia. For example, the local anesthetization of somatic rves markedly depresses the appreciation of visceral pain.

Other Evidence

It has been reported that distention of the stomach (138, 157) and odenum (29) will sometimes reproduce typical distress in peptic ulcer tients.

We have produced pain in the dog by suddenly injecting several cc. of rmal saline solution beneath the mucosa of an innervated pyloric pouch that the mucosa was elevated from the muscularis propria.

Mahlo (158), on the basis of aspirations at intervals of two hours ring the night, states that night pain occurred in spite of acid values excessive as to concentration or volume. He deduces therefrom that d cannot be the cause of pain. None of his data were made available the reader's scrutiny.

Brun (159) believes that the distress or pain in ulcer patients may be

due primarily to vasospasm. He bases this hypothesis on the finding that in these patients the ingestion of 1 to 2 mg. of adrenalin in water or alcohol will bring on the pain, which is then relieved by nitroglycerin. He published two kymographic tracings to illustrate his findings. In the first tracing, supposed to show the production of pain by adrenalin, it appears that the stomach was in a period of active contraction prior to the administration of the adrenalin and continued with the same type of contractions after the drug was given. In the second tracing, purporting to show relief of pain by the vasodilating effect of nitroglycerin, the painful period again coincides with activity of the stomach; these contractions subsided following the nitroglycerin. Thus, the material which the author selected for publication leaves some doubt as to whether vasospasm was involved in the onset of the pain, and whether it was release of such vasomotor spasm instead of gastric muscular spasm which accounted for the disappearance of the pain.

Comment

There will continue to be disagreement concerning the mechanism of pain in peptic ulcer as long as investigators do not establish a common denominator of the type of clinical material and the methods of study. If the issue concerns the question of ulcer pain, then the first two requisites are that the patient have an ulcer and that he have pain. Consequently, these observations should be conducted on patients in whom an ulcer crater is demonstrable by x-ray and at a time when they are having pain. Unless these simple criteria are satisfied, there is no use arguing whether or not the introduction of acid into the stomach or duodenum of an ulcer patient reproduces his distress. Palmer's work has made it perfectly clear that no pain will be elicited if (1) the ulcer has healed, or (2) the acid does not come in contact with the ulcer, or (3) pain is not a feature of the symptoms.

Studies of motility alone will not resolve the problem, since even if the pain appears to coincide with the motility, it remains to be proven that this is independent of the effect of acid. Therefore, the two factors should be investigated simultaneously. The fluoroscopic technique in its present state of development is not the best way to accomplish this, because it does not permit publication of the evidence. If it were possible to make a clear, high speed moving picture of the movements of the stomach and duodenum, together with a flashing light activated by the patient when he experiences pain, and to have this recorded for a period of at least 10 or 15 minutes, during which the patient's abdomen is not manipulated in any way and no conversation is carried on with him, then the fluoroscopic evidence would be available for everyone's inspection. Even

at that the balloon-kymograph method will probably remain superior, because it gives a continuous record for an indefinite period, and in addition to showing the muscular action of the stomach it registers objective evidence of severe pain. Even this method will not record localized spasm of the muscle about the ulcer, which may occur in consequence of the presence of inflammation intensified by acid. Combined with simultaneous sampling or aspiration of the gastric contents via another lumen or another tube, this method is well suited to a study of the relation of gastric and/or duodenal motility to the pain of peptic ulcer. The type of objective evidence which may be obtained by such a method is illustrated in a tracing (Fig. 121) obtained by Dr. Joyce Mason of Dr. H. M. Pollard's laboratory on a duodenal ulcer patient. The information which this tracing conveys is incomplete in that no record of duodenal motility is included. However, it should be stated that this study was not undertaken as an inquiry into the mechanism of pain. Knowing that Pollard was making a study of the gastric motility of ulcer patients, we asked him how frequently he has seen pain in connection with motility phases in these patients. In going back over his records, he found very few instances in which this occurred, but he reminded us that in practically all of his work the acidity was studied simultaneously by continuous aspiration of the gastric contents; thus, in his patients the acid is drawn off quantitatively, or as nearly so as is possible. Pollard has many records showing active secretion and motility stimulated by hypoglycemia in duodenal ulcer patients. In his experience, these patients, when they complain, complain not of ulcer distress but of hunger. But here again the acid is

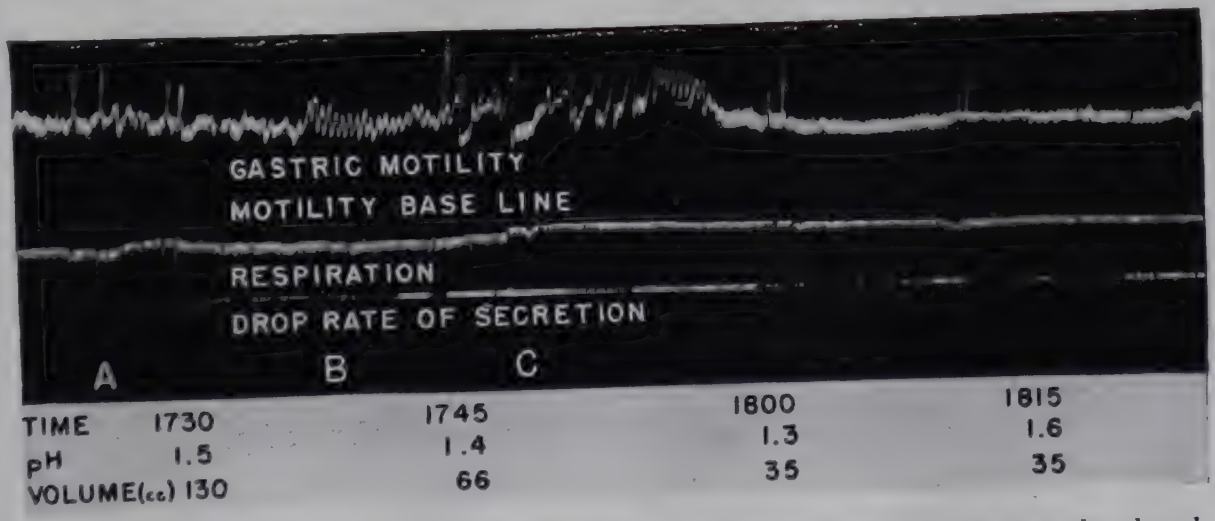


FIG. 121. Tracing showing relief of pain by aspiration of acid in a duodenal ulcer patient, although the tone and motility markedly increased. At *A* the patient was having marked epigastric pain. At *B* the aspirator began to work and the pain began to subside. At *C* the pain was completely relieved. (Courtesy, Dr. H. M. Pollard.)

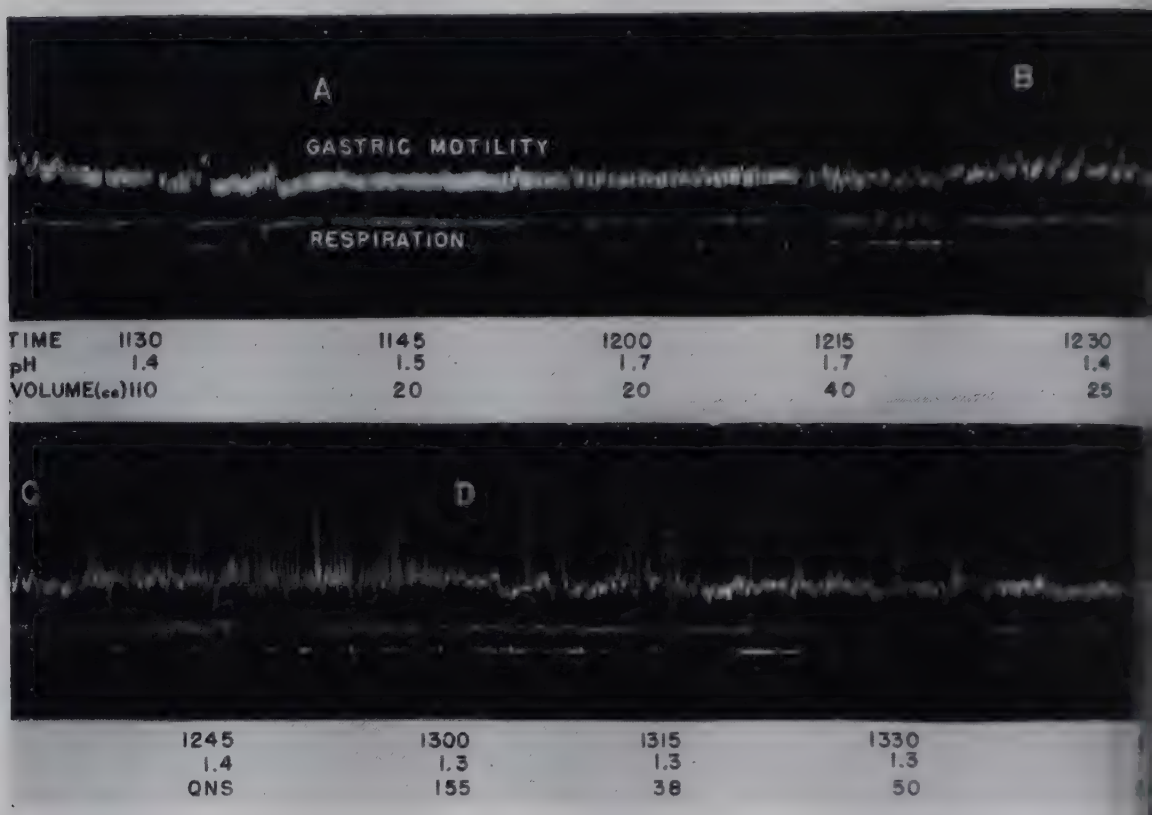


FIG. 122. Pain in a duodenal ulcer patient, precipitated by insulin hy glycemia and relieved by aspiration of 155 cc. of acid gastric juice. At *A* 7 u of insulin were given intravenously. At *B* the patient complained of feeling li headed and weak; blood sugar was 29 mg. per cent. At *C* the patient complai of extreme epigastric pain and moaned loudly; blood sugar was 43 mg. per c the aspirator was not working. At *D* the aspirator was working and the pain completely relieved by the removal of 155 cc. of juice. (Courtesy, Dr. H. Pollard.)

continuously aspirated. Of the three instances which he has been abl find in his records where typical pain was noted on the tracing, (Figs. 121 and 122) occurred in relation to a temporary failure of aspirating mechanism; the third represents an interesting observa (Fig. 123). Here is a graphic record of ulcer pain occurring in associa with strong contractions in the absence of free acid as determined by readings of the aspirated stomach contents, and relieved completel atropine. Had the observers been making a special study of pain, might have introduced dilute HCl at this point.

In the literature, the discussions of the mechanism of pain in p ulcer resolve themselves into an effort to decide whether or not Paln correct in his theory, which he (160) has summarized as follows:

> The pain of peptic ulcer is true visceral pain arising in the ulcer itself. The results from the action of acid gastric juice on inadequately protected tissue accompanying chemical inflammation lowers the pain threshold of the nerves ulcer so that pain may arise from either chemical (acid) or mechanical (peri

pasm, touch, pressure) stimuli. Acid gastric juice is the usual stimulus producing ulcer ain and it is also the eroding inflammatory agent responsible for the lowering of the ain threshold.

This theory must be examined from two angles. (1) Is it supported y the experimental evidence? (2) Does it explain adequately the clinical haracteristics of ulcer pain?

The answer to the first question appears to us relatively simple. 'almer's theory is founded on a great body of experimental work, princi- ally his own, and very little acceptable evidence has been presented gainst it. In particular, those who would disagree with Palmer's ob- ervations and interpretations should at least repeat his experiments *xactly as he performed them;* then it would be possible to determine whether he disagreement relates to the observed facts or to their interpretation.

In answer to the second question, in our opinion the statement that cid gastric juice is the *usual* stimulus producing ulcer pain is compatible ith the clinical manifestations of ulcer pain. At the same time, there are few qualifying considerations which must be kept in mind. First, in the omach, as in all tissues, visceral and somatic, the presence of abnormal onditions, such as edema, inflammation, and congestion, lowers the pain reshold and makes stimuli which are normally inadequate effective. econd, there can be little doubt that the general pain threshold varies om person to person and in the same person from time to time. Third, here is no reason to believe that *all* pain associated with ulcer is due to a ngle mechanism. In connection with the pain threshold, it is well to oint out, for emphasis, that St. John et al. (161), in 2413 fluoroscopic xaminations of 40 year old dyspepsia-free patients who had never had omach trouble, found five with gastric ulcers, 54 with a deformed duo-

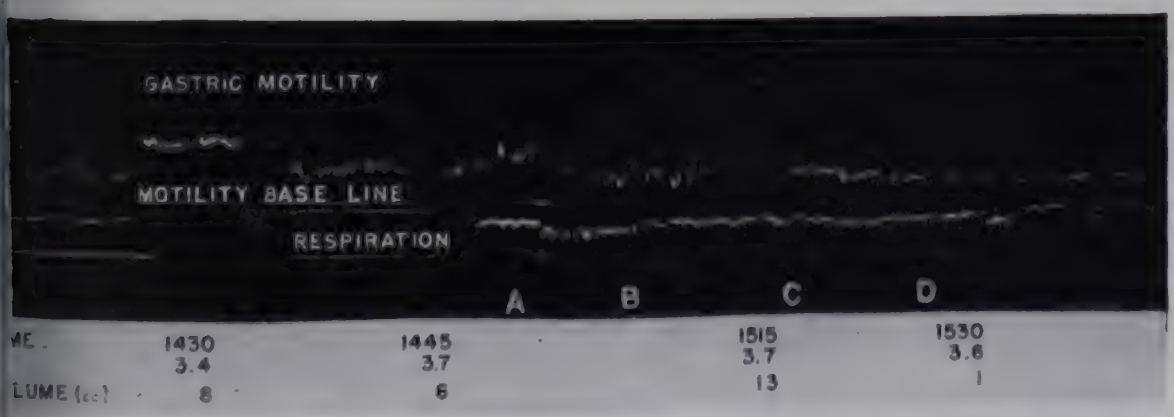


FIG. 123. Pain in a duodenal ulcer patient in the absence of free acid (pH 3.5 greater) and in the presence of active contractions; relieved by atropine. At *A* e patient complained of pain, which became severe at *B*. At *C* 1.2 mg. atropine lfate was given intravenously and at *D* the pain was completely relieved. Courtesy, Dr. H. M. Pollard.)

denal bulb, and even some with craters. Dailey and Miller (162), in 5(asymptomatic males above 45 years of age, found 40 with duoden deformity, 10 of which had craters, and one case of gastric ulcer. Thu there are some ulcers with very high pain thresholds.

It is not difficult to recognize the fact that a stimulus which produc no sensation in normal tissue may evoke pain when applied to damag tissue. Indeed, this is an everyday observation in somatic lesions. That t same applies to visceral organs is evident from our experiments in anima and from those of Wolf and Wolff (163) in man. The latter authors not that when the gastric mucosa of their modern Alexis St. Martin becar engorged and edematous, stimuli such as pinching the mucosa, whi were formerly inadequate, now evoked a painful response. Another a equally important factor influencing painful sensation is the ability of t central threshold for pain to change. It is common observation that men distraction of various types may cause pain to become unnoticed. Pain m be elicited by pressure on an ulcer of the skin and it may also be produc by chemical irritation, such as by acid. Likewise, in the ulcerated gast duodenal segment various types of stimuli may be adequate to initi pain. Furthermore, the threshold may become so lowered by a combi tion of central and peripheral factors that no external stimuli are necess to incite pain; the pain now becomes continuous in character.

In our experience, ulcer patients complain of two principal type pain in the absence of distress due to high grade pyloric stenosis a retention relieved by vomiting. One type is *continuous;* the other is *in mittent.* The continuous distress or pain is described as a sensatior tension, tightness, or lump, with or without a burning sensation. intermittent type may be gnawing or cramplike in nature or it may b intermittent burning or a combination of both. We have seen pati with a combination of both. The continuous type of pain could be du (1) a continuous muscular spasm about the ulcer or the region of the ul (2) an edema stretching the nerves in the margins or the base of the ul or (3) the penetration of acid to the nerve endings or fibers in the mar and base of the ulcer. The intermittent type of pain could be due to contractions on tone or tension, like hunger contractions in cont to digestive peristalsis, (2) digestive contractions on moderate tone in presence of decreased pain threshold due to inflammation secondar acid, (3) localized intermittent spasm about or in the region of the u or (4) a waxing and waning of the neutralization of the acid in the mar and base of the ulcer in consequence of the blood flow.

Although we are convinced that acid is the primary source of pai peptic ulcer, we are not convinced that a motor disturbance is not involved. The patient is usually free of distress in the morning after a

ight's sleep although the fasting residuum may have a free acidity of rom 34 to 60 clinical units. Unfortunately, at present we have no way of lemonstrating the local spasm of muscle about an ulcer. Neither do we ave any data on intragastric pyloric pressure in patients without ulcer. The usual balloon method and radiologic methods are not adequate for uch a determination.

Summary

Analysis of the secretory response of the stomach to various stimuli lepends on the question of the normal range of responses. In this Chapter, he secretory responses of the normal or asymptomatic stomach to a ariety of test-meals and secretory stimuli have been analyzed in terms of heir statistical distribution and "normal" defined in relation to the middle 0 per cent of responses (which includes two probable errors). Hyponor- al and hypernormal secretory responses can then be defined, and these rms have statistical validity.

There is general agreement that the duodenal ulcer patient, regardless f the stimulus employed, tends to secrete more gastric juice than the ormal. This increase is in both volume of juice and its acidity. Gastric lcer patients, according to some reports, tend to secrete more juice than ie normal but less than the duodenal ulcer patient. These relationships old true for basal secretion and, despite discrepancies in the literature, ie best evidence indicates that duodenal ulcer patients secrete more juice night as well. The smaller gastric secretory response of the female to a ariety of stimuli as compared with the male is reflected also in the fact at females have gastric and duodenal ulcers at a lower level of acidity an males. This may be of importance in connection with the remission ulcer during pregnancy, during which it has been shown that the stric secretory response to alcohol or histamine is further diminished.

There is no evidence to answer the question: Does hypersecretion exist ior to the development of duodenal ulcer? There is some evidence dicating that the secretory level of the duodenal ulcer patient does not ange after the ulcer has healed. Pepsin output appears to be increased duodenal ulcer patients but this has no unequivocal etiologic signifi- nce. Mucin secretion is decreased in relation to the amount of acid creted in duodenal ulcer patients. Pancreatic secretion is normal, but e duodenal secretion of Brunner's glands has not been studied in ulcer. ie pH of the contents of the duodenal bulb is more acid in duodenal cer patients than normal subjects.

Theoretically, the hypersecretion of duodenal ulcer may be due to) increased activity of normal mechanisms or (b) superimposition of normal mechanisms. We interpret the evidence as indicating that

normal mechanisms are involved. The mechanism involved may be t release of histamine or a histamine-like substance or the overaction o parasympathetic or cholinergic nervous mechanism difficult to paraly with atropine. Deficiency in the normal buffering or neutralizing mec anism has not been conclusively proven in the peptic ulcer patie The duodenal ulcer patient probably has increased motility and tonic of the stomach, but the nature of the mechanisms involved has not be worked out.

The secretion of acid is essential for the development of postoperat anastomic ulcer, but hypersecretion is not.

Gastric motility is usually not augmented in gastric ulcer, and th is no significant increase in secretion as compared with the normal.

Peptic ulcer in the presence of achlorhydria adequately establis with histamine tests has not been proven to exist.

A seasonal incidence for peptic ulcer exists but reasons for this are clear. It has not been related to upper respiratory infections, to seasc variations in other diseases, or to variations in endocrine factors. It r possibly be related to seasonal variation in gastric secretion.

Radiologically demonstrable gastric and duodenal ulceration r exist without pain. Controversy over the role of acid in the productio peptic ulcer pain has been conducted in terms of a unitary theory of p producing stimuli. While acid is the primary source of pain, evidence e which indicates that motor disturbances are probably the mecha through which the acid causes pain in some patients.

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UTLINE OF CHAPTER 20

Summary

I. Introduction
II. What Is the Nature of the Initial Lesion Which Gives Rise to a Peptic Ulcer?
III. What Are the Causes of Acute Ulcers Which Do Not Heal and May Bleed or Perforate?
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h. Capillary or Arteriolar Abnormality
i. Endocrine Disturbance

E. EXTERNAL ENVIRONMENTAL FACTORS

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b. Population Density
c. Frustrations
d. Marital State
e. Air Raids and War Strain
f. Comment
2. Irregular Living Habits
3. Dietary Indiscretion
4. Dietary Deficiency
5. Smoking, Alcohol, and Caffeine
6. Upper Respiratory Infections and Foci of Infection
7. Seasons

F. MISCELLANEOUS FACTORS

1. Secretion of Brunner's Glands
2. Cause of Pain in Peptic Ulcer

IV. THE TERM "PEPTIC ULCER"
V. IDENTITY OF GASTRIC AND DUODENAL ULCER
VI. ROLE OF ACID-PEPSIN IN THE GENESIS OF PEPTIC ULCER IN MAN
VII. IDEAL APPROACH TO ULCER THERAPY
VIII. SUMMARY

HAPTER 20

Summary

Introduction

In this section of the book, we have attempted to present what is known erimentally and descriptively about peptic ulcer and to examine it for relationship it might have to the etiology of the disease.

Although in Chapter 8 we attempted to present a complete analysis ie genesis of the acute lesion, we did not provide a list of the theories ie etiology of peptic ulcer which have some merit or evidence in their ort. This has now been done in Table 117. At the end of the Table, a of established chronicity factors has been added. It should be noted the intra- and extra-gastric and duodenal factors overlap in many es, as might be expected.

Table 117

THEORIES OF ULCER GENESIS

ntragastric or Intraduodenal

. MUCOSAL DISTURBANCES.

1. Excessive secretion of acid-pepsin and a deficiency of normal neutralizing secretions.
2. Mechanical factors.
   a. Rough food.
   b. Internal and external pressures of organs and clothing.
   c. Peristalsis.
   d. Spasm.
3. Irritants in foods and drinks.
4. Gastritis and duodenitis.
5. Inadequate production of mucus.
6. Natural differences in mucosal susceptibility to acid-pepsin.

VASCULAR DISTURBANCES.

1. Anatomic vascular defects.
   a. Relatively poor blood supply to ulcer-susceptible sites.
   b. Tugging on blood vessels.
   c. Abnormal capillaries.
   d. Infarction.
   e. Arteriosclerosis.
2. Physiologic disturbances.
   a. Vasomotor spasm due to nerves or toxic substances.

II. **Extragastric and Extraduodenal**

A. Constitutional Predisposition.
1. Tendency to excessive secretion.
2. Tendency to spasm of musculature.
3. Tendency to vasomotor spasm.
4. Tendency for stomach and duodenum to be affected deleteriously b
togenic stimuli.

B. Psychogenic.
1. Certain emotogenic stimuli causing excessive secretion, excessive
activity, or vascular spasm.
2. Vagotonia or vegetative nervous system imbalance.

C. Infectious or Toxic.
1. Oral sepsis.
2. Foci of infection.
3. Specific streptococci.
4. Bacterial toxins.
5. Tobacco.
6. Skin burns.
7. Lymph folliculitis.

D. Allergic.

E. Nutritional Deficiency.
1. Protein.
2. Vitamin.
3. Amino acid.
4. Mineral.

F. Endocrine Glands.
1. Pituitary, sex glands.
2. Gastrointestinal—enterogastrone and urogastrone.

G. Neurotrophic.
1. Analogous to the buccal aphthous ulcer or canker sore, which may
neurotic, infectious, or allergic in origin.

H. Chronicity Factors.
1. Mechanical.
2. Chemical.
3. Mucosal susceptibility.
4. Nutritional or reparative.

What Is the Nature of the Initial Lesion Which Gi Rise to a Peptic Ulcer?

The experimental evidence from the laboratory and the de evidence from surgery and necropsy presumptively establishes "chronic" peptic ulcer in man originates from an acute erosion of a nonspecific type. A multiplicity of factors may operate to im mucosa so that an erosion or acute ulcer may develop. Some acu which may become chronic, or perforate, or bleed, are initially nondegenerative vascular disturbance which causes a *focal hem ischemic necrosis* of the mucosa. Congested mucosa, regardless of more susceptible to mechanical and chemical trauma. Some pep

cifically the cinchophen ulcer, start as an inflammation of the epithelial
ls or as a *focal gastritis or duodenitis.* The inflammation may be more or
generalized, but the acute ulcer arises in a focus where the inflamma-
n is most severe.

It has been clearly established in laboratory animals that an acute focal
on of the mucosa is the initial lesion from which develops the "chronic,"
forating, or bleeding jejunal ulcer following gastroenterostomy in the
, the chronic lesser curvature ulcer in the vagotomized rabbit, and the
amine, acid infusion, caffeine, and skin-burn ulcers in various labora-
y animals.

It cannot be concluded that the acute ulcer from which the "chronic"
tric or duodenal ulcer originates is a type of acute ulcer due to a specific
se. For this reason, it is necessary to examine many possible causes of
te ulcer formation and to ascertain those factors (termed "chronicity
ors") which prevent or delay the healing of the acute ulcer.

What Are the Causes of Acute Ulcers Which Do Not Heal and May Bleed or Perforate?

Experimental

Acid Factor. The excessive secretion of acid, particularly in the
nach free of food, is a factor which may be responsible for the formation
cute ulcers which do not heal but bleed and perforate. The stimulation
xcessive gastric secretion in the empty stomach by "sham-feeding" has
caused the production of peptic ulcer; it may, however, if the animal
sham-fed" every hour. Nevertheless, when a large amount of histamine
iven subcutaneously in beeswax, ulcers of the duodenum and pre-
oric and lesser curvature region occur. These ulcers may be due in part
he angiotoxic action of large doses of histamine. However, the instilla-
continuously, day and night, of 1800 to 2400 cc. of 0.15 N HCl
4 per cent) into a dog's stomach while preventing an acidosis by ad-
istration intravenously of an equal amount of base will cause ulcers
he majority of dogs within 10 days. The associated evidence indicates
histamine probably produces an ulcer mainly by causing an excessive
etion of gastric juice.

Two facts are evident from these experiments. First, the concentration
id and the volume of secretion required to cause ulcer within 10 days
ly approaches the maximal capacity of the stomach to secrete. Second,
ulcers which occur are circumscribed or discrete; the mucosa of the
denum or stomach does not slough as a whole. Therefore, *some circum-
ed, local factor of diminished resistance in addition to acid is involved.*

These observations apply directly to postoperative jejunal ulcer, the

cause of which animal experimentation has clearly established. assurance is based on the fact that the possibility of a species diffe between man and dog is avoided because anastomotic ulcer occurs the same frequency in both species after gastrojejunostomy. Anasto ulcer is due to the action of acid chyme on a mucosa, the jejunal m which naturally or constitutionally is more susceptible to acid injury that of the stomach and duodenum. The comparatively low thresho injury by acid may be further lowered by a decreased secretion neutralizing pancreatic juice in consequence of the diversion of some chyme from the duodenum, or by a disturbance of nutrition in quence of a disturbance of intestinal digestion. The occurrence marginal or suture-line ulcer indicates that the mucosal threshold area is reduced by impaired vascularity secondary to connective proliferation or the invagination of mucosa by improper tailorin frequent healing of the anastomotic ulcer when a fistula into the occurs (or into the duodenal loop in the Mann-Williamson dog) in that some factor which predisposes to a relative stasis at the site stoma is also concerned. In most dogs, gastroenterostomy with div of the pancreatic juice and bile to the lower ileum is associated w abnormally prolonged gastric secretory response to a stimulus, as in most duodenal ulcer patients. This exposes the jejunal mucosa buffered gastric juice for an abnormally long period and further stra resistance of the jejunal mucosa. This more prolonged secretion may be due to some jejunitis. It has not been clearly shown to patients with anastomotic ulcer.

Another aspect of the acid factor in the genesis of peptic ulce possibility of a deficiency in the secretion of neutralizing and b secretions. The exclusion of bile or pancreatic juice from the duod followed by the development of a peptic ulcer almost entirely duo location. Such procedures, however, introduce complications a cannot be certain that the ulcer is due solely to a deficiency of neut secretions. There is no evidence to show that a deficiency of the s of Brunner's glands or of the mucous glands of the stomach occ predisposes to ulcer.

Mechanical Factors. It has been clearly shown experiment pyloric stenosis only delays the healing of an acute ulcer and cause it. The etiologic role of "rough food" has been best demo in the vagotomized rabbit, where the incidence of gastric ulcer is approximately 50 per cent by a soft diet.

Irritants Other than Acid. An acute ulcer which does not bleeds and perforates has not been produced by the administr condiments and hot fluids with a reasonable temperature. Me

chemical irritation may stimulate excessive connective tissue pro-
tion in the stomach, which, as in the case of an x-ray ulcer, may delay
ing.

GASTRITIS AND DUODENITIS. The ulcer caused by cinchophen is an
iple of an experimental acute ulcer which does not heal, which may
l and perforate, and which is apparently due characteristically to an
genous gastritis, although in some cases it is due to a duodenitis. A
itis or duodenitis is also associated with the ulcer caused by histamine
eeswax, caffeine, and continuous acid instillation into the stomach.
e evidence of jejunitis is present during the onset of jejunal ulcer in the
n-Williamson dog.

VASCULAR DISTURBANCES. It is certain that the blood vessels of the
ach, from one to all, may be ligated without causing an ulcer to form
ithout delaying the healing of an excision ulcer. However, the impair-
of the blood supply of the mucosa without interfering with the
tion of acid-pepsin, or in the presence of acid-pepsin, results in
ormation of an erosion or an acute ulcer. The mucosal cells must be
uately nourished if they are to manifest normal resistance to acid-
n. The same is true of the tissues in the margin and base of an ulcer.
, when relatively concentrated, may penetrate and injure the walls of
l vessels in the margin and base of an ulcer and reduce blood supply.
schemic and hemorrhagic necrosis due to vascular disturbances have
mentioned above.

NFECTIOUS AND TOXIC FACTORS. Acute ulcers may be produced by the
venous injection of streptococci in animals. These ulcers, unless other
rs coexist, heal and do not bleed and perforate. Many toxic sub-
es have been used to cause erosions and acute ulcers in the stomach.
operate by interfering with the circulation through the mucosa of
tomach and duodenum. They heal unless some other factor con-
e to slow healing is involved.

LLERGY. Acute ulcers of the stomach and duodenum have been
uced on an allergic basis. Such ulcers heal readily.

UTRITIONAL DEFICIENCY. The available evidence does not warrant a
usion relative to the existence of a specific nutritional deficiency as an
gic factor in peptic ulcer. A protein deficiency will cause a gastric or
enal ulcer in some laboratory animals. It has been shown that
iate protein of good quality and the vitamins necessary for good
tion favor wound healing.

NDOCRINE GLANDS. Peptic ulcers occur in dogs with acute or subacute
ial and thyroid-parathyroid insufficiency, and in some species after
jection of large doses of pituitrin. The relation of this to peptic ulcer
an is doubtful.

The reason for the beneficial effect of pregnancy on peptic ulcer h not been adequately explained. It may be due to an increased quanti of a substance in human pregnancy urine which exerts a prophylact effect against the development of postoperative jejunal ulcer in Man Williamson dogs, or it may be due to a decreased secretion of gastric juic

The possibility of the existence of a disturbance of one of the intern secretions of the gastrointestinal mucosa has been studied. Some eviden indicates that less gastric secretory depressant is present in the urine peptic ulcer patients than normal persons. Also, the daily parente administration of an extract of the upper intestinal mucosa for one ye prevented 70 per cent of Mann-Williamson dogs on a special diet fr developing jejunal ulcer. On cessation of the treatment, an ulcer did n appear for from 18 to 48 months, whereas when ulcer was prevented w aluminum phosphate, an ulcer developed within four months after ces tion of treatment. An extract of pregnancy urine has been simila effective in preventing ulcer and delaying its development after cessati of treatment. The active principle appears to be an "anti-ulcer" substa which promotes repair and increases the resistance of the mucosa irritation. It may be derived from the anterior pituitary gland or a mentary tract; its exact source is unknown.

Psychogenic Factor. Practically every part of the brain and spi cord has been damaged in experimental animals, and the vagi a splanchnic nerve supply have been interrupted. Many of these procedu cause a variety of acute hemorrhagic and erosive lesions in the stom and duodenum. However, none of these procedures has given rise c sistently to subacute perforating or chronic peptic ulcers, with the exc tion of the occurrence of a chronic lesser curvature ulcer in the bilater vagotomized rabbit. Ulcers also occur fairly consistently in dogs a celiac ganglionectomy, including perivascular denervation distal to ganglion, a procedure whose applied implications are difficult to visual In view of the clinical evidence indicating that sustained anxiety may concerned in the genesis of ulcer, it would appear that the best appro would be to send a constant stream of impulses over the vagi or splanch nerves. It is known that the continuous stimulation of the vagi for sev minutes to an hour will cause acute lesions in the stomach. Contin stimulation of the splanchnic nerves to maintain a continuous hyper sion has apparently not resulted in peptic ulcer. Attempts to prod peptic ulcer by the induction of neurosis in animals have not been suc ful, but neurotic excitement was only maintained for very short per of time.

Comment. With the exception of the ulcers produced by histam acid infusion, and gastroenterostomy, all of the other ulcers prod

erimentally have occurred in the absence of hypersecretion or of the etion of large amounts of acid. This demonstrates that the ulcers were a large extent due to a decrease in the defensive properties of the cosa.

Although in experimental ulcers both the acid factor and the mucosal stance factor are concerned, we have examples in which the acid factor dominates and others in which a decrease in the defensive properties he mucosa predominates.

Neurotrophic Theory

A neurotrophic genesis is postulated for every disease with an unknown cific etiology. Such a theory has been advanced for peptic ulcer. An te ulcer which may be analagous to an acute ulcer in the stomach is the thous ulcer or canker sore of the buccal mucosa. With this analogy in d, and in view of the possibility that acute ulcers in the stomach and denum may have an analogous etiology, we should outline the little is known about the buccal canker sore (1–3).

Aphthous Ulcer (Canker Sore) of the Mouth in Relation to Peptic Ulcer

These solitary or multiple aphthous ulcers, the common canker sore lyspeptic ulcer of the laity, were described by Galen (A.D. 200), who elated their presence with indigestion in infants. They are usually sified as either acute or chronic recurrent ulcers. The latter group also udes what are called trophoneurotic ulcers. In their pathogenesis, they n as a shallow erosion of the mucous membrane, usually in a mucocal fold or in other locations where they are subject to irritation or ma. The erosion deepens into a shallow ulceration which has a surnding mild inflammatory reaction and which heals by ingrowth of lering epithelium. They may occur in familial situations but do not n to be contagious. A great many factors have been considered onsible in their etiology, but nothing has been clearly proven regarda virus one. Some authors feel that a provocative irritation of the ous membrane in a patient with a predisposition to the disease, i.e., a ific diathesis, is required. Factors of lowered mucosal resistance, gic factors, secondary infection, psychic trauma, endocrine disturbs (especially for those recurrent crops in women associated with the ses), vitamin deficiency, disturbed gastric function, all have been dicated. These canker sores seem to be quite distinct from herpes plex.

A rare subgroup of the chronic variety, the so-called Mükulicz ulcer, id to occur in chlorotic females from 20 to 50 of a "vasoneurotic" type.

It is interesting that these ulcers may follow novocain block for manipulations. This question of aphthous ulcer is raised here becau ulcerations of the mouth, occurring at certain sites of predilect essentially erosive in nature, are influenced by a variety of enviro and host factors, and bear a resemblance to the initial lesion o ulcer. This raises the further possibility that the occurrence of simple aphthous ulcer on the lesser curvature of the stomach, prepy first portion of the duodenum may become a true peptic ulcer u influence of those factors we have listed as chronicity factors. The for more information on the pathogenesis of these simple, comm canker sores of the mouth.

Descriptive Clinical Observations on Natural History Epidmifology

Introduction. The interpretation of the clinical, autopsy, a statistics bearing on the problem of the incidence of peptic ulcer is and uncertain. This is due to many factors which need not be enu here. Even today the clinical, autopsy, and vital statistics vary different hospitals and also among different urban and rural pop in England. Since this occurs, there can be no doubt regard influence of environmental factors on the incidence of the disease

Racial as well as environmental geographic differences in the i probably exist. Further evidence is required to establish and those differences which have been reported. Furthermore, this may be erroneous in view of the fact that the alleged lack of susc of the Negro and Chinese has disappeared under closer study environmental conditions and that the dog, a species remote f but with a stomach much like man's, develops jejunal ulcer with frequency as man after performance of a gastrojejunostomy.

General Incidence. An interpretation of the statistics from navia, Germany, England, and the United States indicates t 5 to 10 per cent of the people in these countries develop a pep during a lifetime. The total number having peptic ulcer with so of activity during any annual period appears to range from 1 to 3 of those above the age of 20. From 0.15 to 0.38 per cent of the p above the age of 20 require hospitalization annually. Among the diseases in the United States in 1937, peptic ulcer ranked tenth a of death, twelfth as a cause of days lost from work, fourteenth a of invalidism, and twentieth as to number of cases. The incide Army of the United States during World War II was 0.3 per c

The mortality from the disease is relatively low, since it has for only 0.65 per cent of deaths in the United States since 1936. I

ent of peptic ulcer patients die from a complication of the disease. ample, in the case of perforation during the last two decades, only per cent of peptic ulcers perforated and only 25 per cent of those ulcers perforated died. Thus, not more than 3 per cent of all peptic atients die of perforations, and since the advent of antibiotics and rgeries, the mortality is probably much less. In the case of hemor- approximately 25 per cent of all ulcers bleed manifestly in the of time, with a mortality of 7.5 per cent or less. Thus, not more .8 per cent of ulcer sufferers die of hemorrhage. The number is ly less since the use of more frequent blood transfusions and the feeding of a soft diet. The mortality rate, however, fails to reveal at amount of suffering, incapacitation for work, and unhappiness by the disease.

ANGING INCIDENCE. It cannot be concluded from postmortem s that the incidence of peptic ulcer has increased since 1850; the e too unsatisfactory. The total postmortem incidence, as reported, fied from 5 to 15 per cent.

ce World War I, the clinical and mortality statistics show that an e in the incidence of peptic ulcer has occurred throughout the This increase has unequivocally involved primarily an increase in idence of duodenal and prepyloric ulcers in males. We believe that rease cannot be entirely accounted for by improved techniques of ation and diagnosis because of a combination of several reasons. crease occurred chiefly in males and only to a slight extent in , and some evidence shows that the increase involved an increase cases as well as the return of old cases. It occurred out of proportion diagnosis of other gastroduodenal disease except gastric cancer. gnificantly, it occurred in the case of perforations for both autopsy nical reports, which have increased since 1910 to 1915 in various es. It cannot be concluded that perforations have increased out of ion to the increased cases diagnosed and to the incidence of reper- s, which now amounts to 1 per cent of all ulcer patients. At the me, all data, whether it be clinical or postmortem, whether it the overall incidence of gastroduodenal ulcer or the incidence of hages, perforations, or stenosis, show that a change in the sex ratio ratio of gastric to duodenal ulcer has occurred. This change ometime between 1900 and 1915. All these facts taken together or have not been adequately explained by assuming that they e to an increased recognition of the existence of duodenal ulcer g just prior to 1915 and to an improved roentgenologic diagnosis enal ulcer introduced in 1921.

autopsy ratio of GU:DU has changed from 7:1 to 1.2:1 since

1900, and the sex ratio has changed from 1M:3F to 3M:1F in the c
duodenal ulcer. It is about 1M:1F in the case of gastric ulcer. We
not found a report of any data pertaining to peptic ulcer since 1
which the condition had a greater incidence in females. For exa
perforation now occurs nine times more frequently in males, whe
occurred more frequently in females prior to 1910. Prior to 1910,
cent of hemorrhages occurred in young women; now hemorrhage
dominates in males.

All lines of evidence establish the fact that the clinical and au
incidence, including perforations and hemorrhages from gastric
decreased dramatically in females under 30 years of age after 1900
must have been due to an environmental factor, the most logic
being the cessation of the fashion of lacing corsets tightly. Tha
believe that peptic ulcer is and always has been primarily a dise
which males are chiefly predisposed.

However, we cannot be nearly so certain that the decided incre
duodenal ulcer in males (and to a much lesser extent in females) w
to some environmental factor other than an increased patholog
clinical recognition of the disease. If it occurred as a result of inc
recognition and has always been present in males to a larger exten
females, we need not search for some unusual environmental factor
than Dr. Moynihan and the x-ray. If an increase actually occurred
we have only to ascertain which factor or combination of factor
supposed to serve as environmental excitatory causes started to
young males shortly after the turn of the century.

Another problem is related to that of the cause of the apparent in
in duodenal ulcer in males after 1900. Clinically, the ratio of the di
of duodenal to gastric ulcer is 3 or 4 DU:1 GU. Yet, mortality st
in the civilian or army population show an approximately equ
tribution, or a slight preponderance of gastric ulcer in some popu
and a slight preponderance of duodenal ulcer in other population
discrepancy may be due to several possibilities: (a) basing the di
of duodenal ulcer too frequently on the finding of a deformed or ir
duodenum; (b) basing the clinical reports more on patients with o
tions requiring high-grade responsibility; (c) missing small du
lesions and scars at autopsy which may have caused clinical sym
(d) missing small ulcers in the stomach with x-ray diagnosis; a
gastric ulcer may be a more lethal disease than duodenal ulcer. Ev
agrees that even a small duodenal or prepyloric ulcer will cause
and more severe symptoms than a similar lesion in the stomach. H
small superficial ulcer could be present in the duodenum, cause de
and symptoms, heal, recur, and never cause death. Also, if death o

some other cause, it might never come to autopsy. Again, it might ithout a scar. The diagnosis of minor lesions of the duodenum by would not account for the increase in the clinical diagnosis of duo- ulcer prior to 1912, bringing the ratio up to 1 DU:1 GU, nor for ne ratio occurring today in certain hospitals in London and Ger- However, the reasons given are perhaps adequate to explain the narked discrepancies between the clinical and mortality statistics. have been unable to find any unusual environmental factor other Dr. Moynihan to account for the increase in duodenal ulcer in young during the period of 1900 to 1915. The x-ray was an unusual nmental factor which certainly accounted for some increase between nd 1935, after which the mortality leveled off. As stated before, we believe that these two factors adequately account for the entire e. Hence, we believe that the increase has been due, first, to the ed recognition of the disease and, second, to the more intense ion of those ordinary environmental factors which serve as excita- uses.

MMENT. This brief discussion of the incidence of peptic ulcer shows factor of constitutional susceptibility is involved, since only 5 to cent of persons contract the disease in a lifetime, and that environ- factors are involved in the pathogenesis of peptic ulcer.

Internal Environmental Factors

NSTITUTIONAL FACTORS. Variation in susceptibility to disease is a biologic phenomenon. If it did not occur in peptic ulcer, peptic would be a unique disease. However, the nature of the constitutional ibility has not been completely defined.

Difference. Sex is a constitutional factor which affects susceptibility tic ulcer and is clearly established. The ratio of male to female and children under 10 years of age with peptic ulcer is 1.3 or 1F. This ratio is the same sex ratio which obtains for most diseases, ng dysentery and enteritis. After 10 to 14 years of age, the ratio of female deaths quickly increases to 4M:1F. After 65 years of age, io declines to that of infancy and childhood. During the age period 15 to 60 years of age, the gastric secretory response of the male eal and histamine is significantly greater than that of the female. ncy very frequently causes a peptic ulcer to enter a remission. act cause of these observations has not been clearly defined. It is to a greater resistance of the mucosa to acid on the part of females, e they have ulcers at a lower level of acidity than do males. The low may account for the low incidence in the female and the remission xisting ulcer in pregnancy may be due to the decrease of gastric

acidity reported to occur in pregnancy. It could also be due to the p in the blood of an increased amount of growth-promoting su during pregnancy.

Gastric Secretion. It has been suggested that peptic ulcer occurs group of persons who constitutionally secrete more acid in respo various stimuli. Too many patients with duodenal ulcer and far too patients with gastric ulcer secrete like non-ulcer patients for this sug to be true.

Age. Although age is important in prognosis, its only rela etiology pertains to the age of onset of gastric and duodenal ulce denal ulcer occurs at a younger age as a rule than gastric ulcer, may be related to the observation that gastric acidity on the ave higher during the third and fourth decades, and gastric secretion to be more involved in the cause of duodenal ulcer than in that of ulcer.

Recurrences. The fact that the majority of patients develop recu in time and that those with complications such as stenosis and hem are more likely to do so establishes a predisposition and is strong e supporting the view that once an ulcer patient always an ulcer pa

Personality Type. Agreement regarding the existence of a personality type in peptic ulcer has not been reached. Such a typ exist in both ulcer and non-ulcer patients, provided some other e factor is concerned and exists in the ulcer and not the non-ulcer p

Anthropometric Measurements. Such measurements have not bee to have a significant predictive value.

Sites of Predilection of Peptic Ulcer. Certain sites are definitely pred to the development of peptic ulcer. *First*, there is the region of t curvature of the stomach, more commonly in relation to the angularis. The predisposition of this area has been demonstrated mentally in the dog and rabbit. Excision ulcers placed in th curvature heal slowly and jejunal patches placed there are more to develop ulcers. This is explained as being due to tugging on, an ference with, the blood supply and greater exposure to me trauma. It is claimed that it has a poorer blood supply as com the remainder of the stomach. *Second* is the prepyloric region, exposed to more mechanical trauma. Also, it is narrow and a is exposed to a larger volume of acid. It is subject to spasm an ference with blood supply. *Third*, there is the first 3.0 cm. of the d on the anterior and posterior wall, which is narrow and is exp large volume of acid per unit area. The chyme is relatively stagna during the entire period of gastric digestion; i.e. the duodenal almost always filled. The blood supply, particularly to the ante

o be relatively poor and subject to embarrassment on tugging
ensic spot"). *Fourth*, jejunal ulcers after gastroenterostomy occur
he first 3 cm. from the stoma, which is exposed per unit area to a
lume of acid. If the gastric contents were directed through the
a or lower ileum, the incidence of peptic ulcer would be very high.
ites of predilection represent constitutional differences in mucosal
bility. They are not always the sole determining factor, however.
llustrated by placing a patch of jejunal mucosa in the wall of the
with a gastrojejunostomy. An ulcer may form in the jejunum
stomach but does not form in the patch. Here, the volume of
ning into contact with a unit area is determining, since all the
me leaves the stomach and only part makes contact with the

anterior wall ulcer is more likely to perforate because of the
of adjacent organs to form a base. Lesser curvature and posterior
ers are more likely to hemorrhage severely because of a more
a location in relation to a large blood vessel.

lary or Arteriolar Abnormality. This is mentioned in this summary
y to indicate the need for further study. The best way to account
circumscribed nature of the acute ulcer caused by acid or any
cerogenic agent is by assuming a local disturbance of the blood
This is clearly evident in the caffeine-histamine ulcer. Therefore,
n that abnormal capillaries are found in the lips and gastric
of ulcer patients is challenging and important. The possibility
acute lesion is of the same nature as aphthous ulcer (canker
the buccal mucosa, a vasoneurotic manifestation, is worthy of
ation.

trine Disturbance. There is no worthy evidence showing that an
e disturbance is involved. If such an endocrine disturbance exists,
have to be related to the growth, maintenance, or repair of the
he mucosa or to inhibiting gastric secretion.

External Environmental Factors

HOGENIC FACTORS. *Occupation.* This factor has been studied to the
antage only recently. In Sweden, it was found that peptic ulcer
gnificantly more frequently in traveling salesmen, tramcar and
employees, and sailors. In England, the incidence of duodenal
d the mortality from it were greater among the men in the high
asses with large incomes and administrative and professional
ilities. The incidence of gastric ulcer and mortality from it were
unskilled laborers. After the age of 50 years, the males with
rative and professional responsibilities had a high mortality from

both types of peptic ulcer. The wives of high-income husbands h
lowest death rate from peptic ulcer. Women who took responsible
or semiskilled positions had as high a rate as any group of men.

In this instance, as is so frequently the case when one analy
environmental situation in human relations, more than one p
contributory factor may be found. The Swedish results were att
to an irregular life and meals. In addition, salesmen and vehicle
are exposed to nervous tensions not unlike those of administrators

Population Density. In Denmark, it has been found that the inc
of ulcer is higher in urban than rural populations. In England, the
rate from peptic ulcer is higher in urban than in rural popul
Numerous differences exist between the two environments.

Frustrations. Difficulties with finances, working conditions, or re
are more frequently an event associated by the patient with the o
ulcer than with the onset of some other physical disturbance, su
hernia. In such instances, it is not easy to control the effect of the p
reading on the answer. For example, in one study, an upper resp
infection was considered to be the cause of the attack in 20 per cen
cases. In a study in England, exposure to cold and dampness wa
by patients as a cause of a recurrence.

Marital State. In the United States, the death rate from pepti
is higher among divorced, widowed, and single males than married
A marked increase in death rate from peptic ulcer occurs in divorc
widowed males between the ages of 50 and 60 years. The only other
studied which shows a similar effect is exophthalmic goiter.

Air Raids and War Strain. During the period of heavy air r
London and smaller towns, the death rate from peptic ulcer increa
did the number of perforations and hemorrhages from peptic u
similar trend was noted in Sweden and Norway during the heigh
war strain.

Comment. We believe there is ample evidence to show that perfo
and hemorrhages from peptic ulcer are increased in number w
population is exposed to an environmental situation in which su
anxiety is an outstanding component of the total situation.

We believe that psychic trauma is an exciting cause of peptic
the ulcer-susceptible person. How it acts to produce an acute ul
to prevent it from healing is uncertain.

The present-day psychosomatic theory of the genesis of pept
is based on three premises. First, ulcer patients manifest a charac
personality pattern or conflict-situation. Second, the emotional
arise is accompanied by or leads to hypersecretion and hyper
or some other abnormality of gastric function. Third, this abno

c function causes duodenal or gastric ulcer. None of these premises
en proved but, in our opinion, deserve much clinical investigation
uantitative type. Since gastric secretion or acidity seems to be the
ring a remission as during an exacerbation in many patients, it
profitable to study motility quantitatively—particularly tone or
ce to distension—as well as secretion.

CULAR LIVING HABITS. This factor is frequently mentioned in the
e and implies irregular eating and sleeping. No one has shown,
, how these factors might affect gastric or duodenal function.

ARY INDISCRETION. This is frequently mentioned as the cause of a
ce or a relapse while under strict management. It may constitute
ing of food, the taking of some prohibited food, as fried meat or
ut, or the drinking of alcohol or coffee.

ugh diet, such as cabbage, carrots, radishes, fresh fruit, or im-
masticated meat, will serve to irritate mechanically a gastric
might affect a duodenal ulcer by favoring a prolonged gastric
response. *We suspect but do not know that it does.*

ARY DEFICIENCY. A diet low in protein may predispose or actually
stric or duodenal ulcer in some populations. This might be more
en mechanical and chemical irritants are present in such a diet.
itamins and minerals which play a role in growth and repair of
ld seem to be of some significance in maintaining the resistance
ls of the stomach and duodenum to injury.

ING, ALCOHOL, AND CAFFEINE. We believe that excessive smoking
ttes is an excitatory cause of peptic ulcer in *some* patients. How
do so is problematic. Alcohol is a stimulant of gastric secretion
oncentrations of 7 per cent or more is an irritant of the gastric and
l mucosa. This is probably the reason why it causes distress or a
ce in some patients and is referred to frequently, like excessive
, as a factor predisposing to perforation and hemorrhage. Caf-
mulates gastric secretion in man and acts synergistically with
e. Like histamine, in very large doses it produces gastric ulcers
Caffeine may play a contributory role in the development of a
cer in susceptible patients, as do smoking and alcohol.

R RESPIRATORY INFECTIONS AND FOCI OF INFECTION. It has not
onstrated by a controlled study that an upper respiratory infec-
excitatory cause of peptic ulcer. One controlled study indicates
sepsis, particularly pyorrhea alveolaris, is associated with peptic
hereas an apical abscess may not be. Further study of this is
l. The evidence of infection of the margin of an ulcer is frequently
The child and infant, which is as subject to upper respiratory
s as the adult, has a low incidence of peptic ulcer.

Seasons. In the United States, the death rate from peptic ulcer reac a significant peak in December and a low mark in August. Signific monthly differences occur when a large number of patients are inclu in a series. This shows that some seasonal factor is concerned though i not a very potent one. When the incidence of peptic ulcer in Australi graphed by months, it yields a curve that is practically the mirror im of the mortality curve for the United States. The cause of the relatio the seasons or months of the year to the incidence of peptic ulcer is pr lematic, though the mucin content of the gastric mucosa is known change in the fall and spring.

Miscellaneous Factors

Secretion of Brunner's Glands. This secretion should be studie relation to the genesis of duodenal ulcer because it is definitely a protec secretion. There is no evidence indicating that it may be disturbed in patient with duodenal ulcer.

Cause of Pain in Peptic Ulcer. While acid is of primary import in the causation of pain in peptic ulcer, evidence exists that the acid operate to initiate spasm of musculature about the ulcer, or to incr the tone (resistance to stretch) of the gastric musculature locally, c the antrum or duodenum to cause a sensation of tension in the epigastr It is well to recall that 0.125 or even 0.2 per cent HCl may be prese the morning gastric residuum of the patient with gastric or duodenal u with the absence of pain, provided the patient has had a good ni relaxing sleep.

The Term "Peptic Ulcer"

Despite its connotation, the term "peptic ulcer" remains the satisfactory one for the ulceration of the stomach and duodenum w we have been discussing. Acid produces the primary injury and p and acid digest the injured cells or denatured fibrin covering the of an open ulcer.

Identity of Gastric and Duodenal Ulcer

We interpret the evidence derived from the experimental and cl observations as indicating that gastric and duodenal ulcer are mani tions of the same underlying disease process. Certain exogenous etio factors determine whether a gastric ulcer develops. The secretion of appears to be more concerned in the genesis of duodenal ulcer mechanical, chemical, or thermal irritation-gastritis producing a appear to be more concerned with the genesis of gastric ulcer.

Role of Acid-pepsin in the Genesis of Peptic Ulcer in Man

The acid factor properly stands first in the list of preferred theories ulcer formation. A considerable portion of this book is devoted to con- ering the role of acid in the genesis of experimental and clinical ulcer. ree facts are outstanding. (a) Experimental ulcers, chiefly duodenal, be produced in the dog when a hydrochloric acid solution closely ivalent in concentration and amount to the maximal capacity of the nach to form hydrochloric acid is continuously instilled into the nach. (b) There is on record no proven case of chronic peptic ulcer urring in a stomach or duodenum of a patient whose stomach per- ently fails to secrete acid in response to histamine. Thus, acid may duce ulcer and some acid is always present in the course of a clinical eration. (c) A few duodenal ulcer patients will secrete close to the ount and concentration maximally possible for the stomach to secrete. On the other hand, certain other facts are equally noteworthy. (a) The rs produced by acid are sharply circumscribed, not diffuse lesions of mucosa and/or muscularis. (b) On studying the acid secretion of a e group of ulcer patients, it is found that a considerable portion of n fall into the middle 50 per cent of the group and some below the n of the group. This is true whether a stimulus is used or whether the ric residuum or the daytime or night-time secretion of the empty nach is assayed. This is especially true of patients with gastric ulcer. The evidence indicates that many duodenal and gastric ulcer patients ete as much acid in response to stimuli during a remission as during exacerbation. Many successfully gastroenterostomized asymptomatic ents will show as high an acidity to a test-meal or as much secretion to mine as they did before the operation. (d) Women develop a duo- l ulcer at a lower level of gastric acidity in response to an Ewald meal men. (e) There are a few duodenal ulcer patients and more gastric r patients on whom two or three histamine tests must be performed re free acid is obtained. (f) Except in the case of a small group of denal ulcer patients who secrete very large quantities of acid, we have ay of predicting which patients will and which will not develop peptic r. (g) The perforation and hemorrhage of an ulcer cannot ordinarily scribed to the excessive secretion of acid, although acid-pepsin is nt and would seem to be essential for the occurrence of these com- tions. (h) The buffering and neutralization of gastric acid undoubt- facilitate the healing of a gastric and duodenal ulcer. These observa- show that acid cannot be the sole factor in the genesis of peptic

ulcer, although it does appear to be a *sine qua non* and is undo
chronicity factor.

Ideal Approach to Ulcer Therapy

This analysis suggests the ideal approach to ulcer therapy an
laxis in the ulcer-susceptible patient. First, some orally active
which specifically prevents the parietal cell from forming acid
found. Second, some orally active substance which increases the
of the mucosa to injury and stimulates repair should be found
gastrone and urogastrone specifically inhibit the parietal cell
must be given parenterally and are not highly concentrated at
time.

Summary

Acute gastric or duodenal ulcer arises from (a) mechanical
trauma, or (b) a vascular disturbance secondary to some toxic
as in burns, or (c) a vasoneurotic, infectious, or allergic mecha
an aphthous ulcer of the buccal mucosa. The acute lesion exten
from healing by (a) acid-pepsin in normal or hypernormal a
(b) mechanical and chemical trauma from rough and irritat
(c) hypermotility or hypertonicity of the musculature. In so
tions, a dietary deficiency is probably concerned. In some case
of excessive amounts of acid causes the initial lesion and preve
healing. In many cases, excessive secretion of acid does not
hence some deficiency in the mucosa must be concerned. In
bland, nonmechanically irritating diet which buffers and neut
should promote healing of the ulcer.

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PART III

The Diagnostic Problem

OUTLINE OF CHAPTER 21

Diagnosis

I. INTRODUCTION
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    2. Nocturnal Pain
    3. Pain and Acidity
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J. ULCER IN INFANCY AND OLD AGE

CHAPTER 21

Diagnosis

Introduction

Considering how heavily we have come to lean on laboratory aids in establishing the presence of a peptic ulcer, it is perhaps surprising how confidently this diagnosis was made in the preroentgen era.

A hundred years ago the great British physician William Brinton (1) taught that the existence of a gastric ulcer could usually be safely surmised by the careful observer. The characteristic clinical picture consisted of: (a) pain of a dull burning or gnawing type sharply localized to a small area in the midline just at or below the ensiform, coming on from two to 10 minutes after the start of a meal, remaining for about an hour, and gradually disappearing, with tenderness persisting in the painful area; (b) vomiting; and later (c) hemorrhage, perforation, or obstruction. This symptom complex was generally considered to be reliable enough to permit differentiation from gastric neurosis and gastric cancer.

Duodenal ulcer offered no problem because at that time it was such a rare disease that Brinton made no mention of it. It was some years before the duodenal lesion began to receive attention by authors writing on digestive diseases. Thus Fox (2), in 1875, mentioned ulcer of the duodenum only to point out that the symptoms it caused differed but little from those of gastric ulcer. However, in certain of his individual case summaries, there are suggestive notations, such as pain occurring when the stomach is empty, excessive hunger sensation, and tenderness in the right hypochondrium. Around the turn of this century, such authorities as Einhorn (3), Ewald (4), Leube (5), Riegel (6), Boas (7), and Hemmeter (8) did not believe that a direct diagnosis of duodenal ulcer could be made with any confidence, nor did they consider it to be of practical importance. In 1900, the Fenwicks (9) disposed of the subject of duodenal ulcer in two pages of a book titled "Ulcer of the Stomach and Duodenum." The inference was that the two lesions differed only in anatomic site, and that practically everything said of gastric ulcer was applicable to duodenal ulcer. The same treatment was given the subject as late as 1911 by Cohnheim (10).

Nevertheless, Moynihan (11), in the first years of this century, de-

scribed duodenal ulcer as a clinical entity and maintained that it presente a distinct clinical picture. He stated, "There are few diseases who symptoms appear in such a definite and well ordered sequence as observed in duodenal ulcer." The simplicity of the diagnosis was illu trated by a statement he made in his book on duodenal ulcer, publish in 1910, namely, "The anamnesis is everything; the physical examinati is relatively nothing" (12). He reported that in 100 consecutive patie diagnosed as having duodenal ulcer, he erred in only three; these thr had biliary tract disease.

Fifteen years later, as a result of the roentgenologic studies of Haud Cole, Carmen, Barclay, Åkerlund, and Berg, Crohn (13) wrote, "Tod no one would care to make a definite statement regarding the site of, even the nature or existence of an ulcerated lesion without the confirm tory evidence of a radiographic examination." As early as 1915, Grah (14) pointed out that on the basis of symptoms alone duodenal ulcer co not be distinguished from gastric ulcer with any degree of precision. A it might be emphasized that much of Moynihan's accuracy was undou edly fortuitous in view of the fact that a major portion of his peptic ul patients had duodenal rather than gastric ulcer.

It is, in a way, paradoxical that with the discovery of radiograp methods, the refinement of gastric analysis, and the introduction gastroscopy, we should still be confronted with major diagnostic proble in peptic ulcer, a disease which formerly was considered relatively e to diagnose. The explanation is to be found in two considerations: fi with the aid of newer technologic methods, we have become more aw of problems which previously were not fully appreciated; and, secc some have expected the technologic advances to replace, rather tha supplement, clinical judgment.

History

The history of the patients' complaints is of prime importance in diagnosis of peptic ulcer for at least two reasons. First, the character pattern of the complaints constitutes the most consistent diagnostic fea of the disease. Second, from the viewpoint of the ulcer patient, his sy toms, except in the presence of complications, constitute the disease.

Pain

Pain, or distress, when present, is the most prominent feature of disease. Moynihan (12) found pain of a characteristic type to be most reliable feature of duodenal ulcer in a series of 100 patients. Fric wald (15) found a characteristic pain to be present in 94 per cent of

ents with peptic ulcer; Miller, Pendergrass, and Andrews (16) found
all of 136 patients in whom peptic ulcer was verified by operation.
The results of surveys made on asymptomatic subjects for the purpose
etecting early cancer of the stomach show that peptic ulcer may exist
ave existed without causing pain or distress in 3.5 per cent of adults
45 years of age. These persons, according to their history, have
r had any pain referable to the upper gastrointestinal tract. In 2913
ents (17, 18) over 45 years of age who had never had any "stomach
ble," six gastric ulcers and 94 deformed duodenal bulbs, some with
ers, were found. The occurrence of painless peptic ulcers is also
enced by the observation that approximately 15 per cent of patients
develop a perforated ulcer or who develop a manifest hemorrhage
a peptic ulcer do so without having a previous history suggestive of
ic ulcer (p. 570).'

Characteristic Pattern of Pain. The pain of gastric and duodenal
r commonly arises after eating. This is true of Brinton's description
e pain of gastric ulcer and of Moynihan's description of duodenal
r. Moynihan wrote:

> ain is generally experienced an hour or more after taking of food, and is referred
> e epigastrium, or right hypochondrium, or indefinitely to the abdomen. I am
> sed to think that reliance may in general be placed upon the time of onset of pain
> licating the position of the ulcer in the stomach or duodenum, and that as a rule,
> earer the ulcer to the cardia the more swift the onset of pain.

Moynihan also considered relief of the pain by taking food or alkali
haracteristic, though not infallible.

riedenwald (15) in 1912, or during the preroentgen era, reported a
of 1,000 patients diagnosed as having peptic ulcer. Of these, 529 had
lenal ulcer; 409 had gastric ulcer; and 62 were undetermined. He wrote
the detection of occult blood was necessary for the diagnosis and that
s generally admitted that pain appearing two hours or more after
s (hunger pain) is indicative of ulcer of the duodenum, while pain
aring early is gastric." In 223 of his patients (22.3 per cent), the pain
ared within one hour after meals; in 188 (18.8 per cent), in from one
o hours; in 491 (49.1 per cent), after two hours; and in 38, irregularly.
he extent of the truth of the claim that the pain occurs sooner after
s in gastric ulcer than in duodenal can only be determined by the
of patients in whom the location of the ulcer has been established by
ation or roentgenographic evidence. We have combined in Fig. 124
data provided by Barford (19) and by Miller, Pendergrass, and
ews (16). Similar but less quantitative data have been provided by
nthal (20). It will be noted in Fig. 124 that the onset of pain occurred

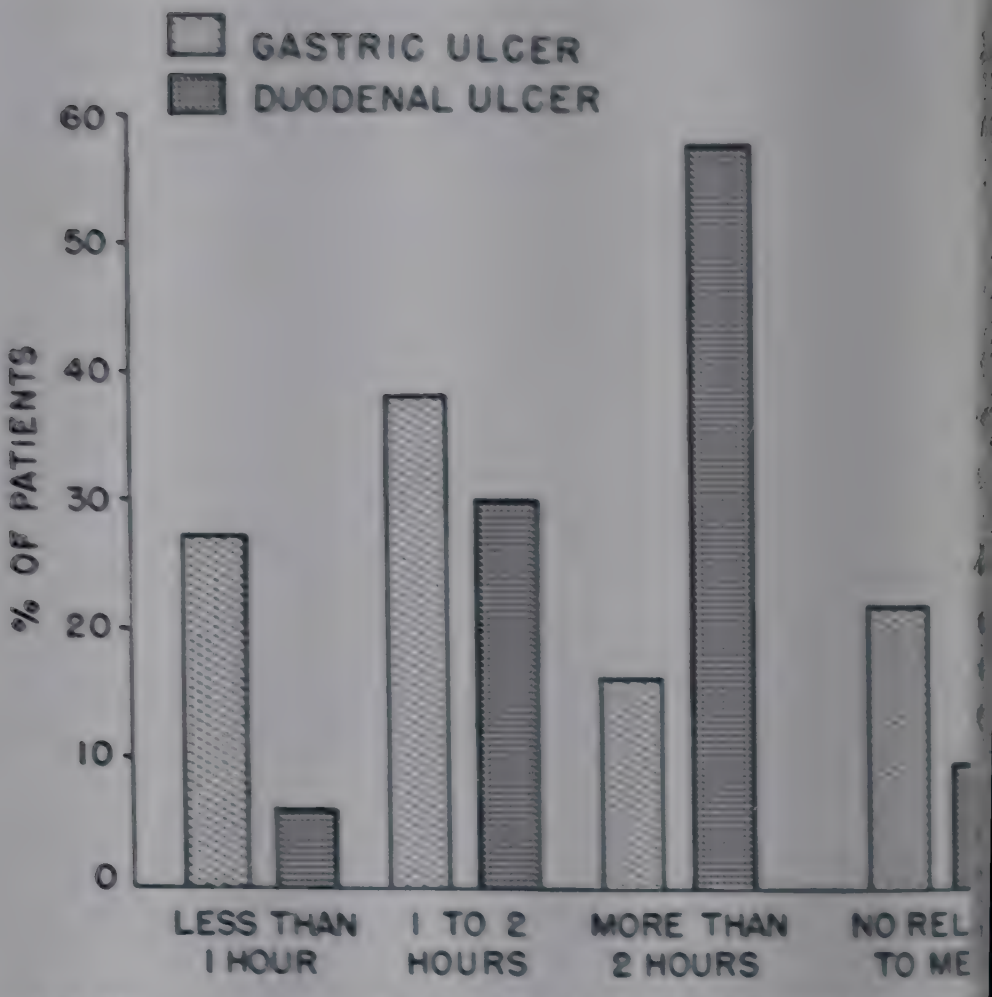


FIG. 124. Comparison of gastric and duodenal ulcer in regard to the t of distress after meals.

after meals in 80 per cent of gastric and 90 per cent of duod patients. In the others, the onset of pain was not related to the of meals. It will also be noted that the pain started two or a after meals in approximately one sixth of the gastric and one duodenal ulcer patients.

Thus, the evidence confirms the generalizations of the clini preroentgen era but shows that the error in applying them w large. Nevertheless, the analysis of a "typical day" as regar important in the diagnosis of peptic ulcer. There is rarely a present before breakfast and it may not occur during the mo have seen duodenal ulcer patients with only nocturnal pain we were consulted.

Wilkie (36) claimed that the absence of a history of "hu was more common in women than men with duodenal ulcer found no confirmation of this claim. Pain may be increa menstruation in some patients. This has been ascribed to a gastric secretion (37).

...ysis. Pain. Pain during the night (11:30 P.M. to 3:00 A.M.) is ... to occur in the presence of gastric retention or excessive intersecretion (night secretion) of gastric juice. It is also commonly ... night pain is more frequent in duodenal than gastric ulcer. ...) states that nocturnal pain rarely occurs unless distress following meal has occurred. Quantitative data supporting these ... are difficult to find. Barford (13) found nocturnal pain to ... per cent of his duodenal ulcer patients and, to his surprise, ... per cent of his gastric ulcer patients. Kirk (128) reported that ... occurred in 91 per cent of 200 duodenal ulcer patients.

...ne Acidity. Friedenwald (15) correlated the degree of acidity ...verity of the pain and concluded that pain was most severe ...ses in which the acidity was high, although it could be severe ...ence of normal acidity of the gastric contents. This is confirmed ... (22). As might be expected, this correlation is not perfect ...

... on Taking Food. The taking of food frequently provides ... relief in peptic ulcer; this applies more frequently to duodenal ... ulcer. When the ulcer is near the cardia, it is said that food ... immediate pain. It is commonly agreed that coarse, raw, irri..., if it does not initiate pain almost immediately after eating, ...the postprandial pain to occur earlier and to be more severe ...

...preroentgen era, food gave temporary relief in 65.8 per cent of ...s diagnosed as having peptic ulcer; it had no effect in 11.7 per ...ggravated the pain in 22.5 per cent (15). In the roentgen ... cent of 556 patients studied by Emery and Monroe (25) ... from food. More recently, the extent of the relief from food ...cer patients has ranged from 71.9 (26) to 90 per cent (27). The ...ata of Barford (13) and of Miller and associates (16) show that ... cent of gastric and 79 per cent of duodenal ulcer patients were ... relieved by food. In some patients, the reported failure to ...he relief after food can be shown to be erroneous by having ... diary of their distress. In others, the reported failure is due to ...ness of the ulcer, food causing only slight relief.

...he taking of food causes early postprandial distress, the possi... distress arising from the colon must be considered. This fact ...n taken into consideration adequately in those reports which ...a on early postprandial pain in peptic ulcer. Some patients ...egrade pyloric stenosis or an hourglass stenosis of the stomach ...istress soon after eating. Pyloric stenosis is probably the most ...se of loss of the characteristic pain picture of duodenal ulcer.

It has been claimed that a "food-comfort-pain" rhythm is characteristic of duodenal ulcer and a "food-comfort-pain-comfort" rhythm characteristic of gastric (28). This is not supported by any quantitative data and is contrary to the usual finding of absence of distress on arising in the morning unless the preceding night was frequently interrupted by pain.

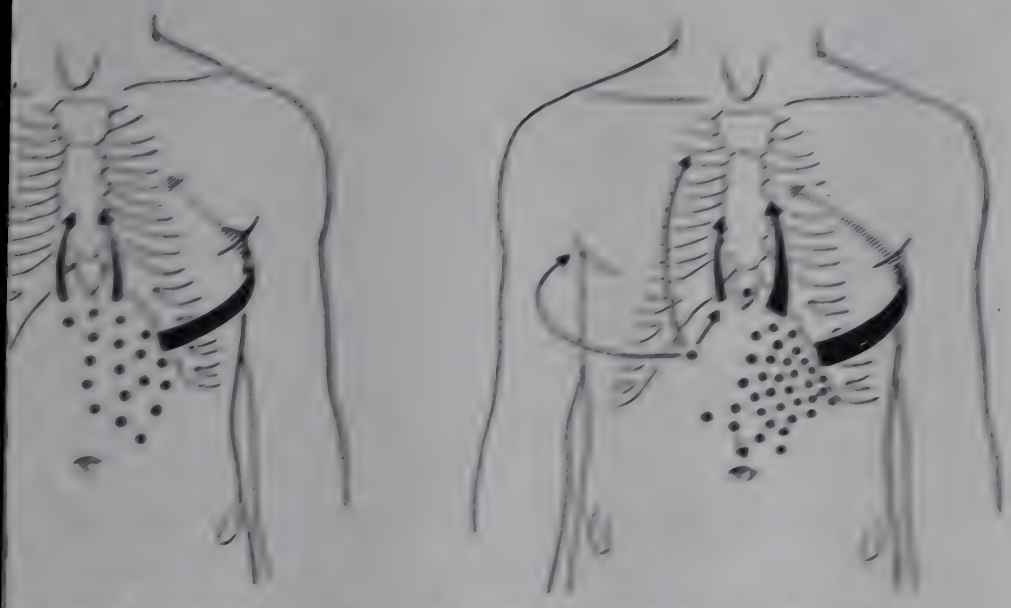
Relief by Alkalies. The taking of alkalies also frequently relieves the distress of peptic ulcer. Seventy per cent of the 556 patients studied by Emery and Monroe (25) noted relief on taking alkalies. Edwin Copeman (26) found that 77.3 per cent of their ulcer patients obtained temporary relief from alkalies. The combined data of Binford (1), Miller and associates (16) showed that only 46 per cent of the gastric and 50 per cent of their duodenal ulcer patients reported temporary relief after taking an alkaline powder.

Frequent Feeding and Antacids. As is well established, frequent feedings of a bland liquid or semiliquid diet such as milk and cream or an antacid is the quickest way of medically terminating the distress or recurrence of gastric or duodenal ulcer. Often the relief may be obtained by the frequent feedings alone. In the case of a "sensitive" or "irritable" ulcer or a penetrating one, the distress is not promptly or completely relieved by both frequent feedings and alkalies. Then, such adjuvant factors as physical and mental rest, rest in bed, the application of heat to the epigastrium, antispasmodics, and sedatives may be required to control and assist in the termination of the distress.

The rapid relief seen frequently after taking food, or lying down, or intravenous injection of atropine argues in support of a vasomotor factor in addition to the genesis of the pain (p. 732).

Quality of Pain. The pain of peptic ulcer is variously described as burning, gnawing, crampike, aching, cutting, boring, sharp, dull, or severe. Some describe it as a hunger pain because it is differentiated by distinguish from a hunger pang and is relieved by taking food. Some describe the distress as a combination of burning and gnawing, and careful questioning will report that a sensation of tension or pressure in addition is present. Sometimes, a sensation of fullness or bloating is noted. But this is more typical of pyloric stenosis. We find no confirmation of the observation that a "burning" sensation occurs more frequently in gastric and a "gnawing" one in duodenal ulcer (14). It is well to recognize that where the pain becomes more severe and constant and more difficult to relieve with the usual methods, it is likely that the ulcer has begun to involve the serosa and/or adjacent organs.

Location of Pain. In considering the pain or distress an attempt should be made to distinguish between the location



(*Left*) Nonperforating gastric ulcers, including subacute ulcers. (*Right*) Perforating gastric ulcers, not including perforation to the liver; the only instance of pain to the right in this group occurred in cases in which the ulcer was close to the pancreas. Each dot indicates the point at which each patient complained distress. Arrows indicate the regions to which the pain was referred. The depth of shading indicates relative frequency of pain shifts. (Reproduced from Rivers. *J.A.M.A.*, **104**:169, 1935.)

by the patient and the location of the point of tenderness on the physician. In the former case, referred pain is involved; in the latter, the pain is perhaps being induced by actual pressure on the nerve endings in the ulcer. The location of pain as described above has been particularly studied by Rivers (29).

If the cardiac orifice of the esophagus, it is generally located beneath the lower end of the sternum and is aggravated by swallowing. When the pain radiates, it is to the left shoulder or upward under the sternum.

If the pylorus of the stomach, the pain is poorly localized by the patient. The point of distress is generally localized by the flat hand to the left or right of the midline when the ulcer is small and shallow. When the ulcer is more extensively inflamed, definite localization is possible in 50 per cent of cases. When the ulcer perforates, the pain is accurately localized in the epigastrium or upper quadrant, usually near the costal margin. Sometimes it shifts or radiates, does so to the back or into the thorax.

If the duodenum, the pain is poorly localized when the ulcer is nonperforating. In those cases (40 per cent) in which the ulcer is perforating, the pain is localized to the midline and right upper quadrant. In 90 per cent of cases of perforating ulcer, the pain is localized to the right upper quadrant, and is

77 per cent the pain shifts or radiates to the back or the region of (Fig. 126). (Duodenal ulcer pain may occasionally be referred t upper quadrant or down to McBurney's point.)

In jejunal or marginal ulcer, the pain is not well localized unless is penetrating or perforating. Then it is generally localized to the above the umbilicus, extending from the midline almost to t margin. The pain tends to shift to the back and also downward foration (Fig. 127).

The careful studies of Miller, Pendergrass, and Andrews (1 indicate that when the referred pain is present in the back, it de the ulcer involves structures posterior to the stomach.

Åkerlund (30) has observed that in some patients the pain of ulcer may first be located in the midline or slightly to the ri midline and then move to the right almost opposite the duod This agrees with the fact that pain from experimental distens first part of the duodenum is felt to the right of the midline (31

Chronicity and Periodicity. The chronicity of ulcer distre known characteristic and is emphasized by such generalizations a ulcer patient, always an ulcer patient." The periodicity of ulcer is also a striking feature of the disease. Seldom do the symptoms over many months; usually they are interrupted by asymptoma which may last weeks, months, or years. The seasonal factor discussed (p. 626).

Pain Sensibility in Peptic Ulcer Patients. The occurrenc or duodenal ulcer, both simple and complicated, without and

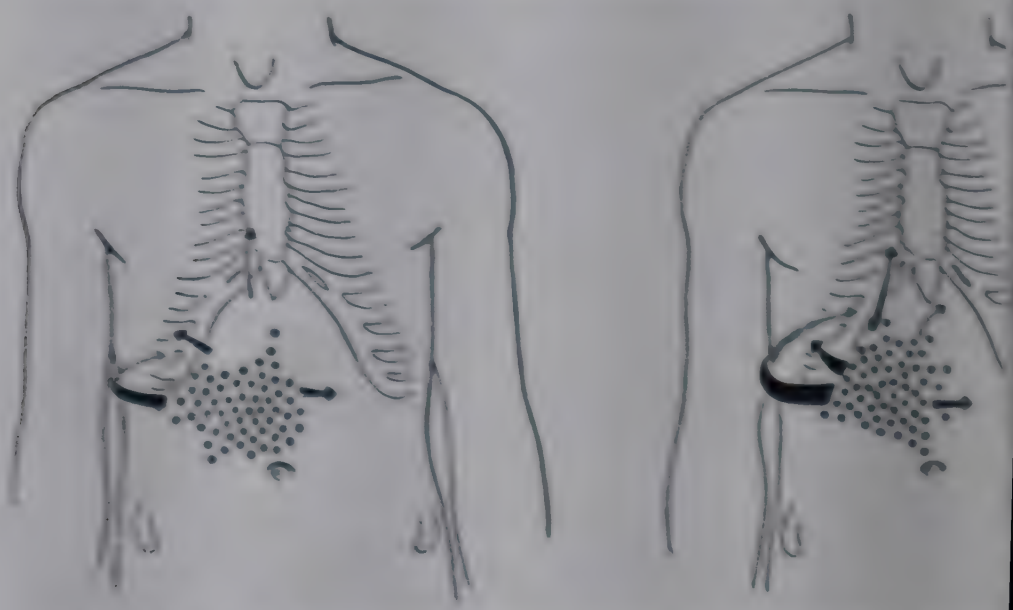
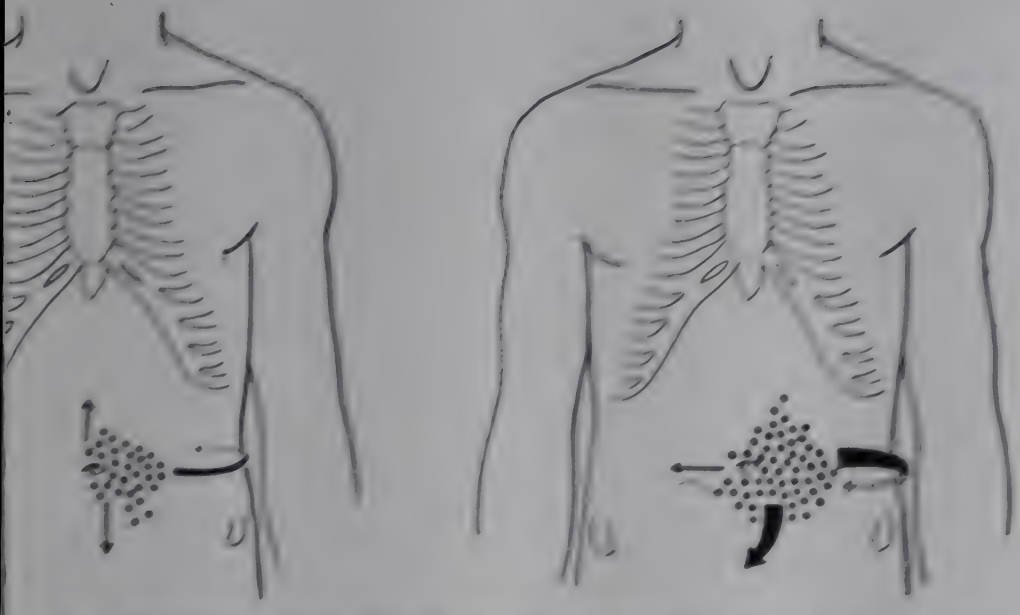


Fig. 126. (Left) Nonperforating duodenal ulcers, including anter ulcers. (Right) Perforating or deeply penetrating duodenal ulcers. S dots and arrows is given in legend to Fig. 125.



(*Left*) Nonperforating jejunal ulcer, including large and subacute (*Right*) Perforating ulcers within or below the anastomosis. Significance of shown is given in legend to Fig. 125.

of pain must also be considered in terms of variations in o pain. Such variation in pain threshold is another example f variation in all biologic material. However, the variation in nitivity of peptic ulcer patients has received very little atten- (35) attacked the problem by applying pressure on the cess. His results demonstrated that peptic ulcer patients were age less sensitive to pain, according to the method used, than ects. The explanation of his findings is probably based on the a rule the presence of pain in one area decreases the sensitivity another area. This subject, however, should be investigated ore recently developed methods of algesimetry.

Vomiting and Nausea

g without nausea is much more frequent than nausea alone. onstrated by the data of Miller and his associates, where of gastric and 68 per cent of duodenal ulcer patients gave vomiting, whereas nausea alone or with vomiting occurred per cent of gastric and 35 per cent of duodenal ulcer ese figures would give the idea that vomiting is relatively peptic ulcer. Statements by authors regarding this point from that of Hurst (33), who writes that vomiting is mplicated ulcer and when accompanied by nausea some ease such as cholecystitis should be suspected, to that of , who reports that vomiting is frequently a part of the he absence of pyloric obstruction, vomiting is most likely to

occur when the pain is severe. At times vomiting, also in the abse
obstruction, may be the chief complaint, a crater being found at
graphic examination. Vomiting obviously is of little differential
nostic value in peptic ulcer because it occurs in so many other cond

Vomiting in peptic ulcer usually indicates the presence of p
obstruction due to inflammatory swelling of an ulcer in close relat
the pyloric outlet, to pylorospasm, or cicatricial stenosis. Such pa
obtain so much relief from vomiting that they learn to vomit at w
provoke vomiting by stimulating the pharynx. Cicatricial stenosis o
standing is usually associated with painless vomiting. In such
visible hyperperistalses frequently occur without pain in the abse
ulcer. So, there must be a difference in this type of hyperperistals
that which occurs in hunger and causes pain; the difference is th
former occurs on relatively low tone or tension and the latter on hig
or tension.

Eructation

Eructation occurred in 58 per cent of the gastric and 64 per cen
duodenal ulcer patients studied by Miller and his associates (16
eructation is frequently associated with the bringing up of sour
contents. Eusterman and Balfour (38) report that "gas" is recorded
history of 77 per cent of their duodenal ulcer patients and 95 per
their gastric ulcer ones. Epigastric flatulence and eructation is fre
complained of in biliary tract pathology and nervous dyspepsia. F
reason, the symptom is of little differential diagnostic value.

"Water Brash"

"Water brash" or excessive salivation in association with the
tation of acid gastric contents is a rather rare symptom in pepti
The salivation is sometimes surprisingly profuse and watery and
tend Stenson's duct so as to cause pain. The symptom, however
characteristic of peptic ulcer.

Heartburn or Pyrosis

This occurs in patients with peptic ulcer as well as in other co
it is characteristic of no disease.

Constipation

Constipation is very frequently complained of by peptic ulcer
It occurred in approximately one half of the patients of M
his associates (16); others state that it is complained of by the
Some patients overlook peptic ulcer distress and ascribe it to con
which they believe requires the daily taking of cathartics. In o

may be normal during remissions and then become spastic so that
us stools may be passed just before or shortly after the onset of a
nce of the ulcer. Some patients will return with alleged ulcer
with no radiologic evidence of a recurrence of the ulcer but with
e of the distress originating in the colon. Quantitative data on the
frequency of these situations is lacking.
rare instances, diarrhea may occur during a recurrence of peptic
When this occurs in the gastroenterostomized patient, a gastro-
olic fistula is occasionally the cause.

Physical Examination

ough the general appearance of the peptic ulcer patient has been
by many observers, the evidence has already been presented
ndicates that no set of anthropomorphic measures furnishes valid
e for a distinct bodily type in the ulcer patient. The supposed
nd hungry look" of the ulcer patient remains a clinical impression.

Epigastric Tenderness

he abdominal examination of the patient with a simple ulcer, the
ding of any significance is localized epigastric tenderness. Bockus
r example, states that if sought for this finding will be noted in
an 75 per cent of patients with active ulcer. Friedenwald noted
per cent of 1,000 cases. Miller and his associates (16) report finding
f tenderness on deep pressure in 57 per cent of gastric and 38 per
duodenal ulcer patients.
tenderness elicited is of two general types. One is due to pressure
on the ulcer from the outside and will be referred to as "visceral
ss." The other is due to a viscero-skeletal reflex and is usually
d with some rigidity; it will be referred to as "reflex tenderness
dity."
ERAL. Tenderness. This can be demonstrated in most cases when
is exerted directly over an active ulcer. Hurst (33) maintains that
lized tenderness persists to some extent until the ulcer heals. In
demonstrate it, the crater must be visualized by fluoroscopy and
applied directly on the crater. This is a visceral tenderness like
d by Palmer and Dragstedt (p. 731) when they exposed an ulcer
ent under local anesthesia and squeezed it between their fingers.
ation of this type of tenderness with reference to the abdominal
ies with the position assumed by the patient. When the patient
position, the ulcer in the stomach or duodenum, unless fixed by
s, will also change its position. So pressure will have to be exerted
site on the abdominal wall, if the ulcer is to be squeezed (33, 34).

Reflex Tenderness and Rigidity. These occur uniformly ulcer perforates or is deeply penetrating. This sign can also be careful examination in many patients in whom the ulcer is penetrating, especially in those patients who localize their pain area and are having considerable spontaneous pain. This area ness has no relation to the position of the stomach and does not a change in the posture of the patient. Hurst (33) states that the is most marked to the left of the midline in the epigastrium curvature ulcer near the cardia, to the right side or bilateral pyloric ulcer, and to the right side "almost invariably" with duod He points out that such a generalization has exceptions. Quant on the relation of the location of the ulcer to reflex tenderness could not be found.

Other Epigastric Findings. As is true of other viscera exaggerated pilomotor, vasomotor, and other segmental re abdominal or epigastric reflexes) have been observed in the epigastrium in association with duodenal and gastric ulcer (32,

Abdominal examination may also reveal scars of previous This is important not only for the diagnosis of the sequelae treatment of peptic ulcer, but also because of the atypical referral of ulcer pain to old abdominal wall scars which may

Laboratory Aids in the Diagnosis of Peptic Ulc

Blood Cell Count. In general, the erythrocyte count is uncomplicated ulcer. The hemoglobin is normal, in the absen ing, although many duodenal ulcer patients have a tendency red blood cell count. The fragmentary evidence of a significant of polycythemia with peptic ulcer has been previously cite The leucocyte count and the sedimentation rate are usually no some complication is present.

Gastric Analysis (41). This has been discussed at considera in a preceding chapter from the viewpoint of the etiologic sig the secretion of acid. A histamine fractional test with several control evacuations preceding the injection of histamine is learn whether the stomach can secrete acid. A standard pr (0.01 mg.) of histamine dihydrochloride should be used. In ga normal patients, the location of the tip of the tube should be fluoroscopic examination to make sure that the tip is not in the distal loop of the small intestine. Sometimes two or more ho are required to demonstrate acid. The cause of such temporary to histamine is unknown (42, 43).

The absence of acid should cause one to question seriously

The collection of more than 30 c.c. of juice during 10 minutes or ged secretory response is definitely suggestive of duodenal ulcer, e important, it indicates that this excessive secretory activity considered in the management of the patient.

all amount of blood in the gastric contents is not very significant, nay come from trauma caused by the tube.

mation of Small for Occult Blood. Leaving the question of ence of hemorrhage aside for a later discussion of complications, ncerned here with the presence of occult blood in the stool of the ith an uncomplicated peptic ulcer. Opinions vary widely on the e and significance of occult blood in the diagnosis of ulcer. Rivers, 21) writes, "Indeed, occult blood is usually absent from the Sackus (35) states, "Almost 50 per cent of patients with active cer of the duodenum seen in my office showed no evidence of eding." Hurst (33) observes, "An active duodenal ulcer (aside y crater) could only be diagnosed in the presence of characteristic e and of occult blood in the stools." In the preroentgen era, some required occult blood for the positive diagnosis of peptic ulcer. hal (26) reports finding no occult blood in the stools of 77.3 per 23 patients with peptic ulcer after they were kept on a diet free and chlorophyl for three days. Barford (19) found occult blood ols by the guaiac and spectroscopic test in approximately 80 per atients with gastric and duodenal ulcer. Page (44) reported that per cent of duodenal ulcer patients the stools were negative for en examined after three days on a diet free of meat and vege- this report, the only criterion for diagnosis was persistent dou- omity, no indication of the clinical activity being given. Many ts might be cited revealing the same discrepancies, which are e fact that the presence or absence of occult blood depends on ctors.

terpretation of the results of the test for occult blood depends et ingested, the amount of blood lost, the length of time the e been on ulcer management, the extent of healing or covering essels with granulation tissue or scar, and a consideration of the blood other than a peptic ulcer.

5) has made a thorough study of this problem. He used the guaiac, and spectroscopic methods for examining for occult 50 normal persons, the spectroscopic test was negative in all, the positive in 68.3 per cent, and the guaiac in 55.3 per cent. On of meat, meat extractives, fish and soup, i.e. hemoglobin-free, lays, the benzidine and spectroscopic tests were negative in all aiac feebly positive in 19.2 per cent of the subjects.

The feeding of five cc. of blood will give positive tests in all norm subjects, but smaller quantities will yield positive tests only in some su jects (315–317). Using dried ox hemoglobin instead of whole blo Kirschen, Sorter, and Necheles (318) found that a larger amount hemoglobin in this form was required to produce a positive test. I found that 1 cc. of blood orally gave a positive reaction in 10 subjects w benzidine and guaiac, and in seven subjects with the spectroscope. E 0.5 cc. of blood orally gave a feeble positive benzidine test in three su jects. Thus, in examining for occult blood in the stool, the diet must hemoglobin-free for three days and gingival bleeding from brushing teeth or bleeding from other causes excluded.

Acid Sensitivity Test or Acid Pain Threshold. Palmer (46) in duced 200 cc. of 0.5 per cent hydrochloric acid into the empty stomac normal subjects and patients with active peptic ulcer. An active pe ulcer was defined as one giving rise to spontaneous pain at some t during the 24 hours prior to the performance of the test. If no p developed by 30 minutes, 200 cc. more was introduced. This was a repeated at one hour, if pain or typical distress had not occurred. W pain occurs, it is relieved by emptying the stomach. The patient is told that the solution introduced may produce pain.

In 30 normal subjects, the procedure caused pain in none, sl burning in one, nausea in seven, and vomiting in four. In 119 active denal ulcer patients, pain did not occur in 16; i.e., false negatives occu in 13 per cent. In 33 active gastric ulcer patients, pain did not occur i.e., false negatives occurred in 24 per cent. In 161 cases of all typ x-ray diagnosed ulcers, false negatives occurred in 16 per cent of case

Hardy (47) applied Palmer's test, with the exception that he rem the gastric residuum at the end of each 30 minutes, in patients with without ulcer. He applied the test 77 times in patients with duoden gastric ulcer having recent spontaneous pain; in 17, or 22 per cen instances no pain occurred. When the test was applied to 71 patients functional dyspepsia, constipation, chronic appendicitis, or cholecy etc. 73 times, pain or distress occurred 15 times; i.e., a false positiv was obtained in 20 per cent of the tests.

Bonney and Pickering (48) and Friedman (27) more recently m study of the acid sensitivity of ulcer patients. The former in all of 1 the latter in all of 33 active peptic ulcer patients observed the produ of pain, though the amount and strength of acid varied from that by Palmer.

It should be mentioned that 0.5 per cent acid may cause a burnin tress or pain in patients with dyspepsia not due to ulcer. The introdu of 0.36 per cent sodium bicarbonate solution will also usually cause d in patients with gastritis, but not in ulcer patients.

Ve believe that further work should be done on the subject of acid
tivity. It may be found to be of differential diagnostic value in those
ents who are having distress in the presence of duodenal deformity and
ie absence of a crater.

String Test. Einhorn (49), in 1909, recommended the use of a
lowed string as an aid in the diagnosis of ulceration in the upper
stive tract. The presence of blood on the string not only indicates an
r but also helps localize the lesion. This method never did come into
use; nevertheless, Einhorn (50) recently reiterated the value of the
g test in cases where the x-ray report is equivocal or not in accord
the clinical picture. We have had no experience with this method.
oretically, it would seem that an ulcer which oozes enough blood to
a section of string should give a positive test for occult blood.

Absorption Test. A substance which, when taken by mouth, would
pass through the intact mucosa but would be absorbed through a
k in the mucous membrane and excreted in the urine would have
in the diagnosis of peptic ulcer. Phenolphthalein was reported by
dman (51) to manifest such properties, but his findings could not be
rmed (39, 52, 53). We know of no further efforts to identify an agent
h would be useful for this purpose.

Roentgenographic and Gastroscopic Methods. It is beyond the
of this book to present a discussion of the techniques of the roent-
graphic and gastroscopic methods for the diagnosis of peptic ulcer.
usefulness and errors inherent to these methods, however, will be
ssed in relation to the problem of the differential diagnosis of peptic
and its complications.

Esophageal Ulcer

his condition occurs so rarely (0.13 per cent at autopsy) that it may
erlooked during the ordinary roentgenographic examination unless
atient complains of substernal pain (54). This is particularly true
ulcer is located anteriorly or posteriorly, which requires that the
agus be viewed laterally or obliquely. Esophagoscopy should visual-
esophageal ulcers.

Gastric Ulcer

Accuracy of Detecting an Ulcerating Lesion in the Stomach

is obvious that an ulcer might be so located in the stomach that it
not be revealed by roentgenographic examination. Accurate data
s question can only be obtained from patients whose stomachs are
ned by an operation or an autopsy. Such data are not readily
ed.

Prior to the introduction of gastroscopy, it was reported that 4.8 p per cent of gastric ulcers were not found on roentgenographic examinat (16, 55). Since the introduction of gastroscopy, several articles have b published providing data on benign gastric ulcer found in gastrosco examination which had not been found by roentgenographic exami tion. Templeton and Schindler (56) by gastroscopy found four gas ulcers in 44 patients (9 per cent) and Renshaw (57) two gastric ulcer 23 patients (9 per cent) which had not been found by roentgenograp Benedict (58, 59), in 71 patients with proven gastric ulcer, found gast copy to be superior to the x-ray in 8.4 per cent of cases. Thus, ro genographic examination may overlook from 5 to 10 per cent of ulcera gastric lesions provided small, nonpenetrating, and healing lesions included.

By gastroscopy, Templeton and Schindler (56) could not visu 15 per cent of 44 cases and Renshaw (57) 33 per cent of 23 cases of pr gastric ulcer. The mechanical improvement of the gastroscope sh decrease this percentage. Significant evidence indicating the percen of gastric ulcers not found by a combination of the use of both metho not available.

Differentiation of Benign and Malignant Gastric Ulce

The outstanding problem in the diagnosis of gastric ulcer today i differentiation of the benign from the malignant form of this le Brinton (1) was apparently satisfied that the distinction posed no se difficulty, for in his extensive experience, he states, only "once or tw have myself met with cases . . . in which there was nothing to justify definite diagnosis between the two diseases . . . ." However, it is ob from his discussion that a reliable differential diagnosis was made or respect to the advanced cases of gastric cancer. On the basis of cli observation *alone* it was not possible then, and it is not possible no make a reliable distinction between a benign and a malignant ulcer enough in the course of the disease to permit a choice of the c treatment. However, from the time of Cruveilhier it has been quest whether such differentiation was of more than academic interest.

Problem of Malignant "Degeneration" of Benign Gastr Ulcer

If carcinoma does develop in a chronic gastric ulcer, then the nostic problem would be negligible. It would suffice only to demon that an ulcer is present. Evidence on this point has been derived several sources.

Experimental Evidence. This is perhaps the only type of ev

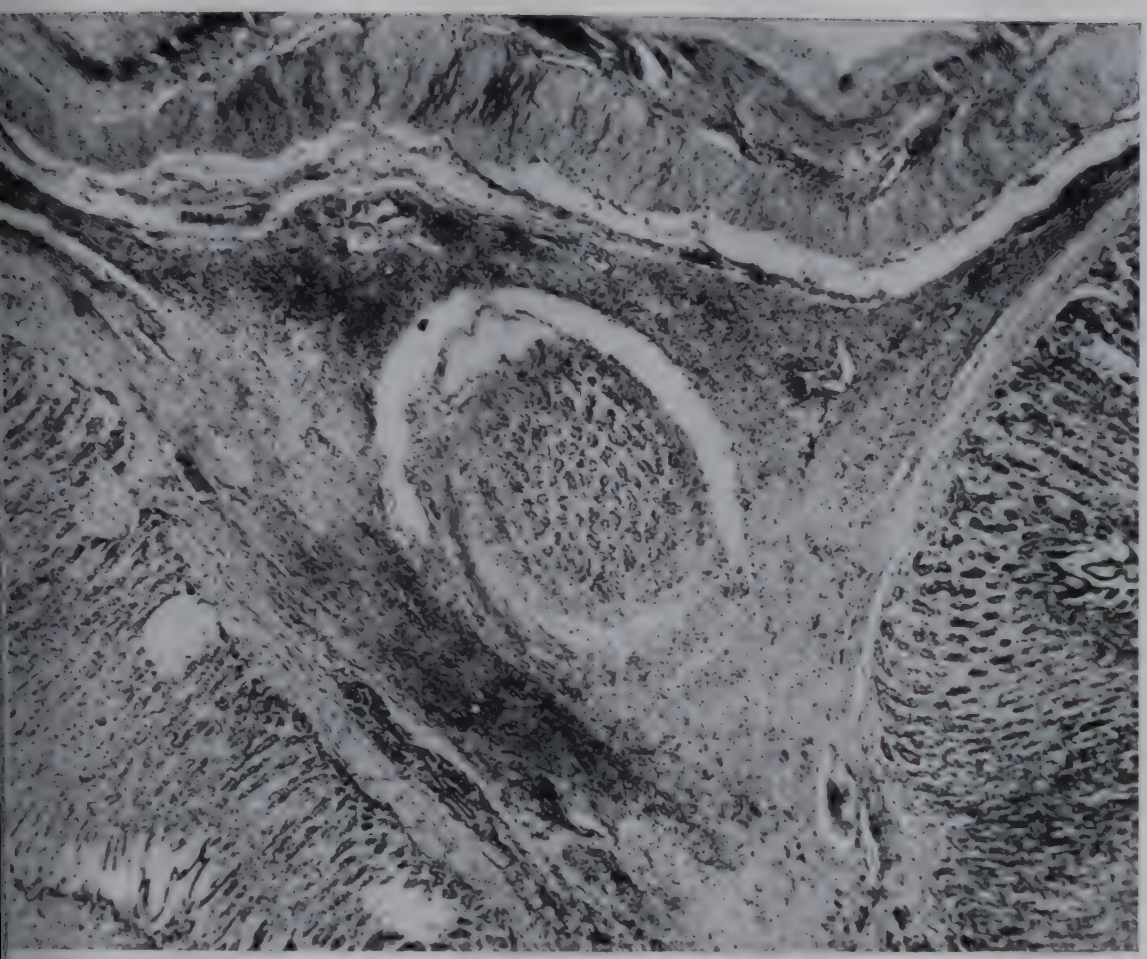


FIG. 128. "Inclusion" of gastric mucosa about a healed gastric ulcer in a rabbit (× 50). Several investigators have referred to changes such as this as indicating invasiveness, but these "inclusions" were found in almost every rabbit with a healed ulcer which was examined. (Courtesy, Ivy and Cooke: *J. Nat. Cancer Inst.*, 5:345, 1947.)

which could answer the question convincingly, yet very little has appeared in the literature to indicate that this method of investigation is receiving adequate attention. The most recent attempt to produce malignant transformation of gastric ulcer was reported by us (60). We selected the rabbit as the experimental animal for this study because it is the only common laboratory animal in which an artificially produced defect of the gastric mucosa leads to a chronic callous ulcer with papillomatous overgrowth of the mucosal edge (see p. 157). We felt that the chronicity of this lesion might increase the opportunity for exposure to orally administered carcinogens, while the tendency toward exuberance of the overgrowing mucosal edge might favor neoplasia. An area of mucosa approximately 1 cm. in diameter was removed from the posterior wall of the stomach and the edge of the resulting defect was oversewn with silk or linen thread to delay healing. Each of the 16 rabbits so prepared received 15 mg. of methylcholanthrene daily, usually in a capsule with 0.1 cc. of benzene but sometimes by hand on a lettuce leaf. We could not obtain any evidence that the

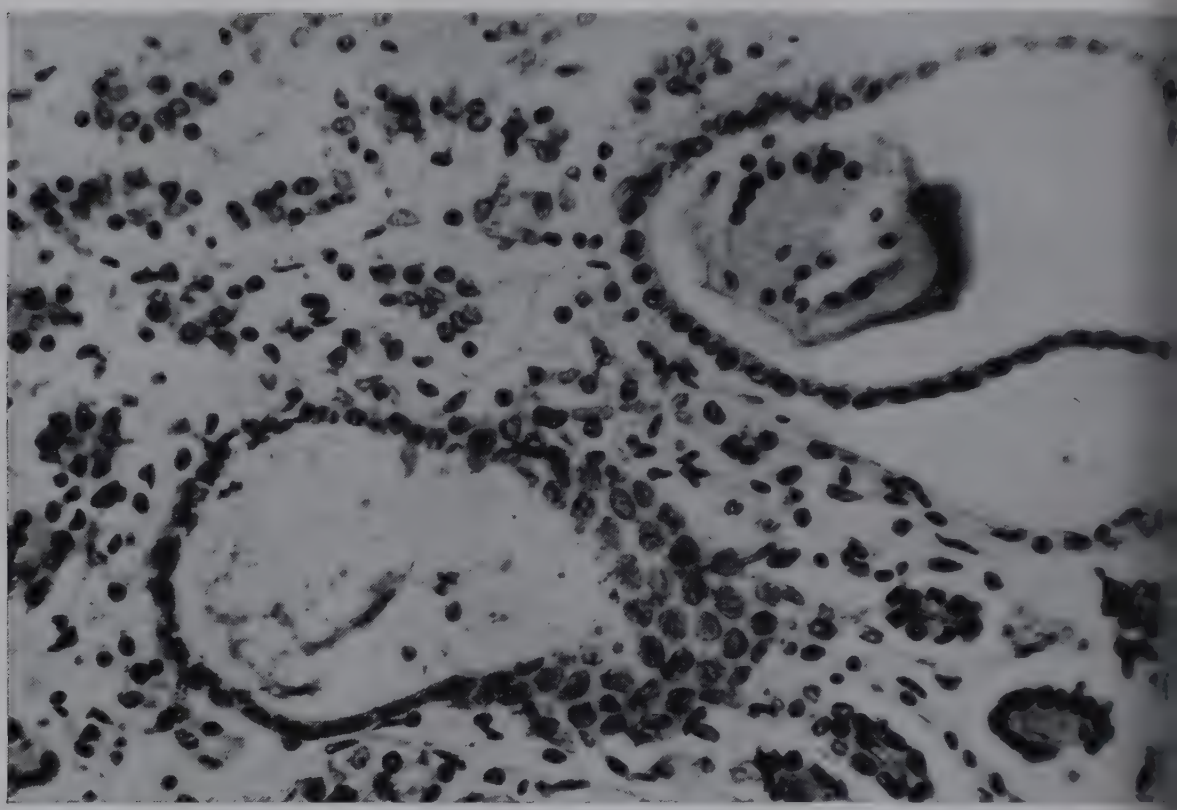


FIG. 129. Example of a change in a portion of the wall of a cyst in the stoma of a rabbit which might be interpreted as invasiveness but which may be the resu of tangential section (× 550).

carcinogen altered the course of the lesions. The phenomenon of "e thelial inclusion" was observed, but we have observed this also to occ in the controls (Figs. 128 and 129).

CLINICAL EVIDENCE. Mayo-Robson (61), MacCarty et al. (62, 63), a Smithies (64) were among those who reported that the majority of gast cancer patients gave a previous history of gastric ulcer. Friedenwald (1 on the basis of 1,000 cases, placed the incidence at around 7 per ce while Taylor and Miller (65) concluded that it probably did not exc 17 per cent. More recently, it was found that ulcer symptoms, with re from food and alkali, occurred as the first symptom in 20 per cent 10,890 cases of gastric cancer (66).

On the other hand, if a significant number of gastric cancers resul from a chronic ulcer, the incidence of gastric cancer in patients with a l history of proven gastric ulcer should be greater than in the general po lation. Crohn (13), on reviewing the literature up to 1927, found t cancer occurred in from 1 to 3 per cent of gastric ulcer patients trea medically or surgically and followed for two or more years (see Brown (67)). Smith and Jordan (68) followed 111 cases of gastric u diagnosed as benign for from five to 23 years. Two, or 1.8 per cent, of gastric cancer. This low figure lends no substantial support to

pposition that a gastric ulcer eventuates in cancer in a significant umber of cases.

Anatomic Evidence. Gastric cancer is more frequently located in the yloric antrum than in the region of the lesser curvature proximal to e pyloric antrum. In a recent report, however, Smith and Jordan 8) found that 17 per cent of 161 ulcers in the region of the lesser curva- re were malignant. This is an unusual finding. Although small gastric cers in the prepyloric region of the stomach are said to be malignant a higher percentage of cases than small gastric ulcers on the lesser rvature, some of the literature is conflicting (p. 510). Cancer of the st part of the duodenum, where duodenal ulcer occurs frequently, is ry rare. Gastric ulcer is present in from 2 to 5 per cent (p. 529) of pa- nts with duodenal ulcer, and gastric carcinoma occurs in only about 1 per cent of patients with duodenal ulcer (69). These observations are t compatible with the assumption that a significant number of cancers ise in a chronic peptic ulcer, irrespective of factors related to the location the ulcer.

Histologic Evidence. Mayo-Robson (61), in reviewing the early erature, stated that the incidence of carcinoma originating in gastric cers varied from 3 per cent in the reports of pathologists of Virchow's stitute to Zenker's conviction that practically all carcinomas originated m ulcers.

In 1909, Wilson and MacCarty (62) published the results of their dies in 153 cases of unquestionable carcinoma of the stomach. Seventy- e per cent presented sufficient gross and microscopic evidence of previ- s ulcer to warrant placing them in a group labeled "carcinoma de- oping on preceding ulcer." Wilson and McDowell (70), in 1914, nilarly interpreted their observations on 170 surgical specimens in which ncer was suggestive or positive (see also ref. 71). Osler (72) questioned criteria for malignancy used by these observers. Ewing (76) considered t malignant transformation occurred in less than 5 per cent of benign stric ulcers. Wilensky and Thalhimer (73) placed the probable inci- nce at 1 to 2 per cent. Stewart (74), studying 70 gastric cancers, be- ed that they originated in an ulcer in 11, or 15.7 per cent, of cases, and nd what he termed malignant changes in 11, or 6.1 per cent, of 180 onic ulcers. Both Stewart (74) and Orator (75) found more malignant nges in the margins of prepyloric ulcers than in the margins of lesser vature ulcers. When Stewart's and Orator's data are combined, per cent of prepyloric and 3 per cent of lesser curvature ulcers mani- ed malignant degeneration according to the histologic criteria they d.

Hauser's (77) review of the incidence of cancer from ulcer illustrated that the European reports were also widely divergent. In autopsy material, the figures ranged from 5 to 30 per cent; in surgical specimens, from 0 to 71 per cent. These variations in the earlier literature indicated the need for uniform and dependable criteria of carcinoma arising in ulcer—a need which was supplied by Ewing (76) and Hauser (77). (See also Col (324).) A frequent error which had been made is illustrated in the photomicrograph of a chronic ulcer in the rabbit (Fig. 128), showing the epithelial inclusions in the base of the ulcer. Such inclusions have been interpreted by inexperienced observers as evidence of invasion.

Hauser (77) described the appearance of cancer developing in ulcer as follows: (a) The lesion corresponds grossly with the typical form of chronic ulcer, that is, a round or oval shape with sharp, even edges and in some instances a terraced floor. Microscopically, there is a sharp delineation between the mucosal edge and the base and the muscularis inclines upward toward, and even into, the edge of the lesion. (b) Cancerous infiltration is absent from the base and is limited to the borders of the ulcer.

The latter point is considered by both Ewing and Hauser to be the most important differential sign, inasmuch as the dense fibrous tissue forming the base of a chronic benign ulcer would prevent the ingrowth of cancerous tissue, and the presence of such tissue in the base must mean that it was present before ulceration occurred.

Hauser lays repeated emphasis on the disposition of the muscularis as a diagnostic aid, because if the lesion is primarily malignant the muscularis becomes infiltrated and loses its flexibility, so that when the tumor tissue sloughs out the muscularis remains fixed, whereas in the benign ulcer the muscular layer is drawn up towards the base.

With the application of these criteria, it has become apparent that the development of cancer from a benign ulcer of the stomach is a very infrequent occurrence, and that if a gastric ulcer is found to be malignant it may have been malignant at its inception. Thus, the problem narrows itself to the differentiation of benign from malignant ulcers.

Differential Diagnosis of Benign and Malignant Gastric Ulcer

In Table 118 are collected several reports in which special studies have been made on the incidence of malignancy in gastric ulcers diagnosed as benign. Of 255 cases subjected to gastric resection with a preoperative diagnosis of benign ulcer, 17.2 per cent had a final diagnosis of carcinoma, 6.5 per cent of 651 medically treated cases eventually proved

Table 118

SPECIAL STUDIES ON THE PRESENCE OF MALIGNANCY IN GASTRIC ULCERS DIAGNOSED AS BENIGN

Author	Surgically Treated			Medically Treated			All Cases		
	No. Cases	No. Carcinoma	Per Cent Carcinoma	No. Cases	No. Carcinoma	Per Cent Carcinoma	No. Cases	No. Carcinoma	Per Cent Carcinoma
ith & Jordan (68)	255	44	17.2	330	15	4.5	600	59	9.8
				Medical					
n & Welch (78)	69	30	43.6	175	13	7.4	267	37	13.8
				Gastro-enterostomy*					
				23	4	17.			
lters & Cleveland (93)	100	19	19.						
d & Priestley (94)				146	14	9.6			
nfort & Butsch (80)							100 (small lesions)	4	4.
terer (311)	628	96	15.2						
mberlain (312)							216	21	9.5
) (313)	193	25	13.						
otal	1345	214	17.2	651	42	6.5	1183	121	10.2

* Not included in medical total.

Total of All Cases Treated

No. Cases	2212
No. Carcinoma	281
Per cent Carcinoma	12.7

to have carcinoma; and 12.7 per cent of all cases collected were actu carcinoma of the stomach masquerading as a benign lesion.

These figures are cited by way of illustrating the seriousness of problem. Experiences such as those reported cast considerable doub the wisdom of attempting to distinguish cancer from benign ulcer demand a careful scrutiny of the present criteria for making this di ential diagnosis.

Roentgenologic Diagnosis. Although it is almost 40 years s Haudek (79) established the niche as a roentgenologic sign of gastric u as indicated above there are surprisingly few good published studi the reliability of the method. Most authorities state that while the ologic characteristics of gastric ulcer usually permit a dependable nosis, there are cases in which differentiation from a malignant ulc impossible. This is readily understandable, in view of the nature of carcinomas, but it would be of definite help in improving diagn criteria if more studies were directed toward quantitating the accu of the x-ray interpretation. In other words, we need more data to pr a firm answer to the following question: Assuming rigid adherence t accepted x-ray signs of benignity in a gastric ulcer, what percenta ulcers diagnosed by the roentgenologist as benign will subsequently p to be malignant?

The first report which we have found that comes close to supp this information is that of Comfort and Butsch (80) in 1937. Their s was based on 100 consecutive cases of ulcer and 100 of cancer, none lesions exceeding 4.4 cm. in diameter. The radiologic criteria wer described; however, the fact that the Mayo Clinic has consistently le toward surgery for gastric lesions suggests that if there were any qu about the benign characteristics of a gastric ulcer, it was more lik be reported as a "lesion" than as a benign ulcer. Even then, the s revealed that when the roentgenologist made a diagnosis of benign the pathologist found cancer in 7 per cent (see also ref. 66). *Of cou question arises whether the pathologist's diagnosis of cancer was correct*, beca the uncertainty of a histologic diagnosis in the absence of metastases At any rate, the problem needs to be approached along these lines we get some accurate conception of how often a malignant lesion stomach is diagnosed as benign. If this occurs in a significant pro of patients, then the erroneous cases should be reviewed for the p of determining whether certain hitherto acceptable x-ray criteria reality unreliable as signs of benign ulcer. Only in this way c radiologic differential diagnosis of ulcer from cancer be improved.

The pathologic and clinical evidence certainly shows that the percentage of greater curvature lesions are malignant.

Gastroscopy. According to Schindler (81), an experienced gastros-
st can readily recognize whether a gastric ulcer is benign or malig-
in all but exceptional cases, assuming that the lesion does not happen
ccur in one of the areas not visualized by the gastroscope. Schindler
not give any percentages except to state that the experienced gastros-
st can make the diagnosis in 90 per cent of the cases. He has person-
only twice made the mistake of calling a malignant ulcer benign;
in view of an experience running into thousands of gastroscopies and
ably hundreds of ulcers, is ample testimony to the reliability of this
od in the hands of an expert.

Comparison of Roentgenologic and Gastroscopic Methods.
e are several reports comparing or correlating the diagnosis made
oth of the examinations on the same lesions. Schindler (81) contends
gastroscopy is more accurate, although still not infallible. Chamberlin
is of the same opinion, but others (57, 83, 84) call attention to the
ent mistakes of both methods. Benedict (58, 59) expresses the senti-
s of many when he emphasizes the complementary, rather than the
petitive, roles of the two types of examination. More data designed
swer the question that follows are needed. In a consecutive series of
ic ulcers which the roentgenologist diagnoses as benign, how many
iagnosed by gastroscopy, and subsequently proven, to be malignant?
haw (57) found in 60 cases of the differential diagnosis of a benign
malignant lesion that both examinations agreed in 27 cases, the
oscopic being indeterminate or incorrect 13 times, the roentgenologic
indeterminate or incorrect 12 times, and both incorrect 8 times.
dict (58, 59), in 144 cases of cancer of the stomach, found both
ods of examination to be correct in 77 cases, doubtful in 11, and
rect in 4. In the remaining cases, x-ray was superior in 32 and
oscopy in 20.

Moersch and Kirklin (83, 85) have pointed out by a study of 100
ed cases (cases where the roentgenologist asked for the opinion of
astroscopist) of proven gastric cancer that gastritis is most frequently
sed with cancer. The error was 10 per cent. In five cases, the gastros-
called a malignant ulcer benign; this mistake was made 14 times
e roentgenologist. In 10 cases, the surgeon was uncertain regarding
xact nature of the gastric lesion.

hus, when both methods of examination are used to differentiate
en a benign and malignant ulcer, the result may be incorrect in
0 per cent of cases and doubtful in an additional 15 per cent.

Gastric Analysis. The available evidence (86) indicates that in a
nt with an ulcer of the stomach, a persistent achlorhydria to hista-
(0.01 mg. per kg. body weight) rules out a benign lesion. Emphasis

must be placed on the necessity of *repeated* tests. Our experience coinc with that of Palmer and others in showing that a transitory histan achlorhydria may occur in the presence of a benign gastric ulcer. is true even though the tip of the gastric tube is proven fluoroscopic to be in the stomach. The diffuse gastritis which may be seen ga scopically or in the resected specimen in such cases makes the tempo achlorhydria understandable. We have seen several instances in whi basal anacidity persists until considerable healing of the ulcer takes pl after which free acid begins to appear in the fasting gastric secretion

Thus, the presence of free acid does not rule out a malignancy, bu repeated absence of acid on stimulation with histamine rules o benign ulcer. Otherwise, gastric analysis is of no differential value unless the free HCl in response to a test-meal is 80 units or greater; the ulcer is almost certainly benign (80).

Site of Lesion, Age, and Size of Lesion. It has been previously sh that most gastric carcinomas, as a whole, occur in the prepyloric pa the stomach, whereas most benign ulcers occur on the lesser curva Similarly, it has been reported that a high percentage of prepyloric u or craters are malignant (319). Allen and Welch (78) found 65 per ce ulcerative lesions of the prepylorus to be malignant while only 10 per on the lesser curvature were. All greater curvature ulcers were malig but only 20 per cent of those on the anterior or posterior wall and 1 cent of those in the pyloric canal were malignant. Orator (320) fou (50 per cent) of 30 prepyloric ulcers to be malignant whereas only 6 cent) of 300 lesser curvature lesions proved to be so. Stewart (321) five (25 per cent) of 20 surgical specimens from the prepylorus to b cerous ulcers, whereas only 12 (5 per cent) of 260 on the lesser cur had that diagnosis.

On the other hand, statistics from other clinics do *not* show a pre tion for carcinomatous ulcers in the prepyloric part of the sto Ransom (97) found that eight (10 per cent) of 78 prepyloric ulcers malignant and at the same time seven (8 per cent) of those from the curvature were also malignant. Smith and Jordan (68), in their op material, found that 15 (17 per cent) of 98 lesions in the prepyloru malignant, whereas 27 (17 per cent) of 161 lesser curvature ulce were malignant. Fifty-five per cent of craters elsewhere in the st were malignant ulcers. The discrepancy noted in these statistics is pr due to sampling errors related to the selection and the fewness of c each series.

It is evident that many craters in relation to the greater curvatu cardia are actually cancer. Although there may be a greater perc of malignant ulcers in the prepyloric than in the lesser curvature the difference is not great enough to be helpful diagnostically.

Alvarez and MacCarty (322) at one time wrote, "Gastric ulcers larger
n a quarter and carcinomatous ulcers smaller than that are . . . rarely
ountered . . . ." However, they found that 23 per cent of carcinomas
cted at the Mayo Clinic fell within the range of the diameter of benign
rs (3.7 cm.). The experience of others has been somewhat different.
n and Welch (78) found that 2 per cent of gastric ulcers less than 1 cm.
iameter were malignant, 20 per cent of those 1 to 2.5 cm. were malig-
t, and 45 per cent of those 2.5 cm. or greater were malignant. Graham
3), in 24 prepyloric carcinomas in which ulceration was the only find-
found 17, or 71 per cent, in which the lesion was less than 2.5 cm.
s, a sufficient percentage of small ulcers are malignant as to render it
lvisable to place considerable faith in the view that all small ulcers are
gn.

Gastric ulcers which have produced symptoms for only a short time
t be suspected of being malignant. But Allen and Welch have shown
in a significant number of patients a carcinomatous ulcer may be
ent even when symptoms have been present for many years. In pa-
s with dyspepsia for five years or more, 18 to 48 per cent of gastric
rs were malignant, depending on the age group.

That sex is of little or no diagnostic value is indicated by the statistics
nith and Jordan. The ratio of males to females was 3.2:1 for malignant
ic ulcers and 2.2:1 for benign gastric ulcers.

Carcinoma is generally a disease of advancing age. However, 11 per
of carcinomas occur in patients below the age of 40 (38). Although
malignant ulcers occur in elderly individuals, Allen and Welch have
n that carcinoma may masquerade as a benign disease in a significant
ber of patients less than 40 years of age. Ransom found the average age
atients with benign ulcers to be 52.2 years and that of those with
gnant ulcers to be 56 years.

Test of Healing. Probably the most popular procedure in the diag-
of gastric ulcer is the therapeutic test as described by Jordan (87).
consists of a period of rigid medical care in the hospital, during which
he symptoms must subside *completely*, (b) occult blood must disappear
letely from the stool, and (c) the crater must disappear *completely* and
valls of the stomach at the site of the lesion must regain their normal
lity and pliability. In addition, the patient must remain symptom-free
discharge from the hospital, and a followup examination must show
gn of recurrence of the lesion. In Jordan's series of 133 patients with
ic lesions, 67 that were not immediately diagnosable as malignant
given a trial of medical therapy. Complete healing took place in 44
; in the remainder, surgery was advised because of failure to heal and
najority of these cases proved malignant. As a result of Jordan's
am, no malignant ulcers in this series were neglected, while at the

same time 44 patients were spared an unnecessary operation. In v
this record, Lahey (88) at that time urged a careful test of healing
gastric ulcers before resorting to surgery.

Questions soon arose as to the reliability of the therapeutic tri
diagnostic measure. Rivers and Dry (89) cited a case of healed ulce
ultimately proved to be malignant, but it is to be noted that this c
not fulfill Jordan's criteria, inasmuch as the symptoms did not com
abate. Gray (90) and Eusterman (91) reported additional cases t
trate the danger of accepting disappearance of the crater as evid
benignancy. Similar experiences were reported by Scott and Mide
Allen and Welch (78) described a case in which complete heali
gastric ulcer, verified by x-ray and gastroscopy, occurred under r
management, yet operation revealed a carcinoma of the lesser cu
with involvement of lymph nodes. Wilensky and Thalhimer (7
others have reported a similar experience.

There is thus a legitimate question concerning the dependabili
therapeutic trial in the diagnosis of gastric ulcer. The seriousness
problem cannot, however, be assessed in the absence of quantitativ
For example, there is some difference of opinion as to what co
a reasonable therapeutic trial. Hurst and Stewart (33) make t
nouncement that if an ulcerative lesion of the stomach does not d
completely in three weeks, surgery is required without delay. Ot
content with a definite reduction in the size of the ulcer after a
period of rigid management, followed by disappearance on suc
examinations. From what is known of the biology of healing o
(Chap. 6), three weeks would certainly be a minimum period in w
expect complete healing, and this presupposes ideal conditions; he
insistence of Jordan (87) and others that the therapeutic trial be
out in a hospital. The matter is further complicated by the fac
benign ulcer under treatment may be shown radiologically to
larger before it becomes smaller, due to the resolution of ede
inflammation around the mouth of the ulcer and to the entrance
barium into the crater.

These considerations dictate a need for application of clinic
ment based on a clear understanding of the nature of the healing
rather than application of inflexible rules based entirely on the exc
case where the diagnosis turned out to be in error. There is no do
a malignant ulcer may appear to heal completely. The mechanis
phenomenon is readily appreciated if it is recalled that a sma
may slough out almost entirely, especially in the presence of a g
centration of acid, leaving an ulcer with only a small remnan
cinomatous tissue—a process suggested by Brinton (1). Such a le

o a considerable degree, by the same principles of healing as apply rimary benign ulcer. But the important question is: How frequently this phenomenon occur? Eusterman and Balfour (38) stated, "It pe taken for granted that, with the rarest exceptions, if complete mic restoration and symptomatic recovery occur, the lesions are n." But according to Walters et al. (66), the complete disappearance astric ulcer which subsequently proves to be a cancer occurs in "an ciable number of cases." It would be highly instructive to have itative information on this point.

AGNOSIS BY SURGERY. Diagnosis by surgery implies a partial gastrec- since an accurate microscopic diagnosis requires that numerous n the periphery of the lesion be examined. In other words, whereas edical test of healing seeks to diagnose what type of lesion the patient e surgical test diagnoses what the patient *had*.

e arguments in defense of diagnosis by surgery are essentially two- irst, if the surgeon or pathologist cannot make the diagnosis with ty when he has the stomach open and can see and feel the lesion, an anyone attempt to make a reliable diagnosis with any instrument f the microscope? Second, the penalty of temporizing with malig- lcers is greater than that of operating upon benign ulcers.

e first argument is so easily recognized as a *non-sequitur* that it s little comment. It is entirely possible and indeed probable that an n an intact stomach may exhibit characteristics at fluoroscopy or at copy or by other diagnostic procedures which make these examina- ore reliable than an examination of the gross specimen. To take a example, the survey of 200 small gastric lesions by Comfort and (80) revealed that none of the malignant lesions occurred in the h with a maximal concentration of free HCl of 80 units or higher onse to a test-meal, whereupon they concluded that a concentration than 80 clinical units is almost a certain sign of benignancy.

to the second argument, it appears to us to be futile to engage in a versy that can only be settled by facts which have yet to be estab- Walters and Cleveland (93), in a paper emphasizing the risks of l treatment for gastric ulcers, quote a prominent internist as follows: convinced that the mortality and morbidity which would accrue in g these early lesions surgically would be far less than a similar large f cases handled medically." In the interests of scientific progress in ne, it would be highly desirable to have access to the evidence upon such convictions are based. This evidence must relate to the two f the argument, viz., (a) the morbidity and mortality of a large f small gastric ulcers handled medically and (b) the morbidity and ty of a comparable series handled surgically.

In a series handled medically, the matter of accurate diagnosis is to l considered. Here it is difficult for us to formulate any convictions from t available literature. Taking the data from a single large, efficient clinic an example, we may note the following figures: According to Rivers a Dry (89), it was "surprising" how many mistakes were made in the dia nosis of benign and malignant lesions. According to Walters and Clevela (93), "In a recent study of 100 consecutive cases in which small, pr sumably benign gastric lesions were removed, the lesions in 19 were fou to be carcinomatous on pathological examination." Walters (95) stat that 10 per cent of gastric carcinomas were diagnosed as benign. Judd a Priestley (94) found that 9.6 per cent of 146 patients treated medically f gastric ulcer for from five to 12 years developed gastric cancer. Comf and Butsch (80) wrote, "When the diagnosis of benign ulcer was made, t diagnosis was correct in 96 per cent and incorrect in only four per cent cases." This illustrates the difficulty of arriving at a conclusion as to h many cases of malignant ulcer are liable to be neglected by an effort differential diagnosis. The figures from the same clinic range from 4 19 per cent. If the true average error in diagnosing a malignant ulcer benign is 11 per cent, the error in different groups of 150 ulcer patie would by chance or random sampling range from 4 to 20 per cent. So, range of 4 to 19 per cent appears to be a true range. The mean actu corresponds closely to the mean of 12.7 per cent collected from many cli (Table 118).

As to the morbidity and mortality of handling these early les surgically, we shall make a further comparison with the series exami by Comfort and Butsch, in which 96 per cent were diagnosed as beni Suppose that no effort at radiologic differentiation were made, and tha small gastric ulcers were subjected to surgery. According to the rela incidence, a maximum of 20 of the 100 lesions resected would probabl malignant. Now, according to Walters et al. (66) and Pack and Living (96), even in cases where no gross metastases are present, the five cures amount to no more than 20 per cent. Therefore, only 20 per cen the above 20 malignancies would be cured, that is, 4 cases. This is exa the number of malignancies which were missed in the series of 100 u diagnosed as benign. So, we see that according to this evidence, 96 of cases of small ulcers could be spared surgery by efforts to make a diff tial diagnosis, with the same end result as if all 100 were operated u without an attempt to reach an accurate diagnosis. On the other h 50 per cent of five year cures might be obtained by early operation; 90 cases out of 100 would be spared an operation by making a differ diagnosis.

If, however, all of these cases could have been resected without

lity and morbidity, it could be argued that the risk of an error in agnosis does not justify medical treatment. This requires an examination the second facet of the argument, namely, the mortality and morbidity gastric resection. The study of Ransom (97), dealing with cases operated on at the University of Michigan Hospital, showed unsatisfactory sults in 8 per cent (persisting symptoms in 5 per cent and jejunal ulcer in per cent). This is in addition to a mortality, for all gastric ulcers, of 7.9 r cent. However, this study covers a 20 year period, and recent improvements in technique and the use of antibiotics and sulfa drugs undoubtedly make the above figures excessive. Judd and Priestley (94) ported an operative risk of 2.5 per cent for gastric resection for gastric cer. In another recent paper, Smith and Jordan (68) reported an operative mortality for 255 cases of gastric resection for malignant and benign stric ulcer of 2.7 per cent and a total hospital mortality of 5.9 per cent. 111 cases treated medically and followed for five to 23 years, two 8 per cent) died of gastric cancer, and four (3.6 per cent) of unknown ıses, giving a total mortality of 5.4 per cent, which compares favorably the total hospital operative mortality of 5.9 per cent.

Recent improvements in technique and the use of antibiotics and sulfa ıgs undoubtedly render the above operative figures somewhat excessive. example, Lahey (98), who now apparently advocates resection for all tric ulcers, reported a mortality of zero in the resection of 110 consecu- cases. The morbidity figures were not given. In addition, it is argued t gastric resection is a more effective therapy for gastric ulcer than dical management (94).

Summary. We believe that the question is still open pending further estigations of the type suggested in the foregoing pages. The policy in tain quarters of operating on all gastric ulcers can neither be defended condemned on the basis of existing evidence. However, such a policy have great merit if the operations are carried out only after thorough lication of all the measures useful in making a differential diagnosis, this would be the therapy par excellence to answer this question: How ırate is the diagnosis of benign gastric ulcer? The following items argue avor of a gastric ulcer being benign: youthfulness, high acid, lesion on lesser curvature less than 2.5 cm. in diameter, roentgenologic and roscopic opinion of benignancy, and favorable immediate response to lical management.

Duodenal Ulcer

Introduction

Prior to the refinement of the radiologic examination of the duodenum, diagnosis of duodenal ulcer was made essentially on the history of

recurrent attacks of a characteristic symptom complex. Moynih
described the clinical picture as follows: (1) Pain, described by the
as boring, gnawing, or burning, coming on two hours or more aft
and relieved by eating (hunger pain). The pain awakens the pa
night, usually about 2:00 A.M. (2) The appetite is preserved. (3) Ve
is infrequent.

Moynihan (11, 12) reported that the above history alone was su
basis for surgery and in his experience a duodenal ulcer was foun
per cent of cases. This evidence is the type that is hard to controve
in fact, as far as we can discover, no one has yet presented acceptat
which can seriously challenge this part of Moynihan's work. That t
the classical history can be elicited, the diagnosis is one of the most
it is possible to make in medicine. His accuracy was also increased
fact that most of the patients he saw had duodenal rather than
ulcer. Cases have been reported (99, 100) in which, although the sy
of duodenal ulcer were present, no ulcer could be demonstrated e
operation or by roentgenologic examination. However, these pub
do not make it clear that the cases in question answered the
described by Moynihan.

The parts of Moynihan's teachings which subsequent experi
modified are: (1) All, or practically all, duodenal ulcer cases a
acterized by the above symptoms. (2) "Hyperchlorhydria" is syn
with duodenal ulcer. For instance, he wrote, "I have never operat
a case of protracted or recurrent hyperchlorhydria without t
duodenal ulcer." (3) The treatment of chronic duodenal ulce
always be surgical. Partly because the latter two concepts wer
accepted and followed on the continent and in the United St
operation of gastroenterostomy was all too frequently performed
viduals without ulcers.

The fact that some cases of duodenal ulcer do not prese
symptoms constitutes one aspect of the diagnostic problem. T
aspect lies in the fact that *a remission of the symptoms may not mean
the ulcer and, conversely, a recurrence of symptoms may not mean reulcer-
duodenal mucosa.* The diagnostic goal has, therefore, been to per
tive methods for the demonstration of the ulcer. The following
will indicate to what extent this goal has thus far been reached.

Gastric Analysis

Throughout the years, and especially before the x-ray di
duodenal ulcer came into widespread use, efforts have bee
identify a gastric secretory pattern specific for this disease, as
other diseases of the upper digestive tract. That these efforts ha

y rewarded is illustrated by the fact that each new gastric secretory
has been eagerly tested for its differential diagnostic value. No
pose would be served by reviewing the enormous literature which
imulated, covering the studies with various test-meals, or with
histamine, and caffeine. The results published by some of the
workers (101–110) on this problem show that while an excessively
prolonged curve of acid secretion is a common finding in duodenal
cers, the same type of curve may occur in non-ulcer individuals

gastric analysis might be of value as an indication that the ulcer
n patient has healed, if Shay (111) is correct in his supposition that
olding curve" is due to the ulcer and surrounding inflammation.
ot, as well as other aspects of the acidity in duodenal ulcer, has
ussed before (pp. 692 et seq.) and we concluded that a fractional
nalysis is no more informative than an examination of the basal
, and that the latter measure is diagnostic of the presence of an
the duodenum only in the case of the upper few per cent of
who secrete more acid than is ever found in normal persons.

Roentgenologic Diagnosis (112, 113)

DEFORMITY OF BULB. Frequently, the radiologic report of examination
per gastrointestinal tract concludes with a statement somewhat as
"Constant deformity of the duodenal bulb without definite
of crater." When the patient has been referred for x-ray examina-
ause of digestive symptoms, what is the significance of such a

dy after Holzknecht (114) visualized the first part of the duo-
nd termed it the duodenal bulb, Cole (115) published his classic
owing that induration or cicatricial contraction surrounding the
an ulcer produces a constant deformity of the bulb. Cole did not
how often the operative findings in these cases disclosed a healed
tead of an open lesion. Although Chaoul and Stierlin (116)
lear that the deformity may mean a scar, as well as a crater, the
logic diagnosis of duodenal ulcer was generally made whenever
ty of the bulb was present. More than a decade after the impor-
he duodenal niche had been established, Kirklin (118) said, "I
t radiologists are justified in interpreting deformity without a
duodenal ulcer, leaving it to the clinician to determine whether
t is suffering from an active ulcer at the time of the examina-
is is equivalent to saying that duodenal *deformity must arise* a
past ulcer, a statement which is amply supported by the available
Cole (115) reported that in a series of more than 500 cases

presenting constant deformity of the duodenum, the diagnosis of duod ulcer was proven by surgery. Miller, Pendergrass, and Andrews diagnosed duodenal ulcer in 100 cases and at operation found the u healed in four; thus, the error on this account was 4 per cent. Accor to Kirklin (118), the error in diagnosing duodenal ulcer on the basi deformity amounted to less that 4 per cent. More recently, Somervell (1 wrote, "I can recollect only 3 cases in the last 500 or so in which a formity of the duodenal cap, which was found to be persistent du several fluoroscopic examinations, did not indicate duodenal ulcer." latter observer had an unparalleled opportunity to study the relatio deformity to ulcer, inasmuch as he operated on these patients routi as soon as the diagnosis was established (see p. 313).

It is only in exceptional instances that duodenal deformity is bro about by adhesions secondary to inflammation of surrounding org Kirklin (119) reported a number of cases in which duodenitis prod deformity sufficiently resembling that caused by ulcer to lead to a mist diagnosis. For all practical purposes, however, the roentgenogra demonstration of a constantly *deformed duodenum means that the patient either an ulcer or a scar*. There remains the further diagnostic proble attempting to determine which of these lesions is present, an endeav which radiology has made great progress in the past two decades.

Niche or Crater. The reports of Åkerlund (30, 122) and Berg (were the culmination of determined efforts to refine the diagnosis of denal ulcer by direct demonstration of the crater. Åkerlund accompli this by devising equipment with which he could obtain film exposur the duodenal bulb under varying degrees of compression and i possible projections. To anyone interested in the radiologic diagnos duodenal ulcer, the monographs of Åkerlund and Berg are indispen reading. To what degree their contributions have enriched this fie evident to anyone who has had an opportunity to compare the com sion method with the conventional technique.

Åkerlund (30) reported that a niche could be demonstrated in 6 cent of cases of duodenal ulcer. Following the publications of Åker and Berg, Carman and Sutherland (124) took the position that the pression method did not add much to the diagnosis because in most of ulcer seen by them the bulb is so characteristically deformed nothing is to be gained in looking for a niche. Kirklin (120) later a that if a niche is present it can be seen by roentgenoscopy just as well compression roentgenography. In a series of 1658 cases of duodenal Carman and Sutherland (124) were able to see niches in only 13 per Kirklin and Burch (120) discerned a niche in 38 per cent of 100 c duodenal ulcer regarded by the clinician as active at the time of

mination. They considered that this ratio was not far below the maxi-
m possible, for among 73 cases of active duodenal ulcer examined in
opsy specimens, less than 50 per cent had craters that were potentially
nonstrable as niches. The earlier studies of Berg (123) led to a somewhat
erent conclusion. Berg reasoned that every duodenal ulcer where the
el of the lesion differs from that of the surrounding tissue should be
nonstrable as a niche, and contended that corroboration of the x-ray
lings should not be in the cadaver but in resection material soon enough
r the radiologic examination that healing has not progressed too far.
ll cases where these conditions were fulfilled, he found complete agree-
nt between the presence of a niche at x-ray and the finding of an ulcer
er in the resected specimen.

At the time of Berg's report in 1926, he considered that a niche was
nonstrable in 60 per cent of cases. Geyman (125), by using the newer
niques, raised the incidence of niches in his material from 22 to 64 per
t. In Åkerlund's (122) later report, he mentioned the presence of a
e in 75 per cent of his cases. In Templeton's (126) experience, the
re is about 65 per cent. Friedman (127) puts it at 80 per cent. Several
r recent reports (128, 129) give values of 60 per cent of 200 cases and
per cent of 195 cases for crater visualization. The evidence thus points
n ever increasing efficiency in the direct radiologic demonstration of
crater.

The importance of these advances is that the niche remains the only
ct roentgenologic sign of an ulcer, and the more dependably the ulcer
f can be demonstrated, the more accurate the diagnosis. This is of
e than theoretic significance. For example, in the matter of deter-
ing the recurrence rate in duodenal ulcer patients, one must distin-
h between recurrence of symptoms and recurrence of ulcer. The two
t recent studies (130, 131) of recurrence rate in duodenal ulcer were
d on exacerbation of symptoms, although in both reports the authors
mented on the difficulty of determining what degree of exacerbation
ymptoms should be regarded as a recurrence. This is a problem in
h the x-ray demonstration of bulb deformity alone is not of much help
e clinician. Moreover, in the extensively deformed and irritable bulb,
presence of pouches or sacculations secondary to old scarring may lead
e erroneous diagnosis of a niche (120, 132). The confusion engendered
pasm may, according to some authors (127, 133), be overcome by the
of large doses of atropine, but the differentiation of scars or pseudo-
rticula from craters may be impossible. Teschendorf (133), for
nce, presents two illustrations of duodenal flecks appearing to be
rs but shown at surgery to be scars, and he states further that often, at
ation, pseudodiverticula were demonstrated where he had diagnosed

niches. Emery and Monroe (134) could not recognize any un
differences between the contour of the ulcer-bearing and the scar-be
bulb, and they concluded that it was not possible to make an acc
diagnosis of healed ulcer by roentgen examination. Likewise Temp
(126) states that the deformity does not change appreciably in mo
stances even though the ulcer undergoes exacerbations and remiss
These are further examples of the limitations of the x-ray diagnosis
the latter is based on deformity alone, rather than on the demonstrati
a crater.

So, since the precise diagnosis depends on the visualization of a
and since the frequency with which the niche can be demonstra
cases of active ulcer is not known, we cannot fully agree with Barclay
that in the hands of experts the diagnosis of duodenal ulcer has adv
to little short of mathematical certainty, nor with the similar sen
expressed by Enfield (136).

The main problem in evaluating the efficiency of the x-ray exami
is the lack of a check on the radiologic diagnosis. A limited study
paring the roentgenologic with the histologic findings in duodenal
was made by Sutherland (137), who concluded that the pathogno
roentgenologic sign of ulcer is the niche. If an expert radiologist,
proper equipment, were to examine Somervell's (121) ulcer p
(p. 804) who, because of the conditions, are operated upon immed
it would provide ideal conditions for quantitating the accuracy o
visualization. It would also help to settle certain points of disagre
such as the important question of whether an ulcer always prod
deformity of the bulb. It is generally assumed that if the radiologist
a diagnosis of a normal bulb, a duodenal ulcer is ruled out. Cla
Geyman (117) contend that the absence of bulbar deformity do
preclude the possibility of an active ulcer. Åkerlund (30) takes a c
position in the matter; he writes, "Every open ulcer of the bulb
extends more deeply than the purely superficial defects of the
membrane in fresh acute ulcers causes an alteration in shape or
of the opaque contents of the bulb, which by the help of an exq
careful technique, when practiced by an experienced radiologist,
tically always roentgenologically demonstrable." Lacking a study
type mentioned above, we know of no way to solve these probl
present.

Other questions are: To what extent can duodenitis cause d
deformity and symptoms simulating those of duodenal ulcer (11
the presence of a scar causing deformity predispose to the devel
of symptoms simulating duodenal ulcer in the presence of duode
psychosomatic disturbances?

Anastomotic Ulcer

Introduction

e development of an ulcer at or near the anastomosis after a gastro-tomy or gastric resection is usually indicated by pain or hemorrhage a or hematemesis). In those patients destined to develop an motic ulcer, these symptoms develop within one year in 50 per cent thin two years in 70 per cent. Though the chances of an anastomotic eveloping decrease with time, one may develop 10 or 20 years after cration (Table 119), or even 38 years later (138).

anastomotic ulcer occurs on the average earlier after a gastro-tomy than a subtotal gastric resection, according to the meager ce available (Table 119). However, at two years 70 per cent of the destined to develop after both gastroenterostomy and resection have o.

ough an anastomotic ulcer may occur at any age from two to 2), it is more likely to occur in younger individuals. Anastomotic is seen more frequently in males than females. In 1227 cases ed by us, 1123 occurred in males and 104 in females, yielding o of M:F of 10.8:1, which is greater than the sex ratio for al ulcer (M:F = 4 or 5:1) (p. 612). However, this does not mean ales are more likely to develop anastomotic ulcer, since the litera-es not provide data on the relative number of males and females enterostomized.

Symptoms and Signs

N is the most frequent symptom and is said usually to be more than that of gastric or duodenal ulcer (33). In Wright's (142) series cases, only 20, or 4 per cent, had no pain, and a jejunocolic fistula esent in 14 of these. Others reporting on a much smaller series found be absent in from 9 to 27 per cent, melena being the chief symp-these (148–150).

e pain is generally referred to the left of the midline and just above he level of the umbilicus, according to our observations. Such was e in 75 per cent of the patients of Eusterman and Balfour (38). ght's collective inquiry (142), the pain was reported to be located "epigastric" region in most cases (approximately 60 per cent), the right of the midline in only 5 per cent of cases. It was found to t of the midline in 20 per cent of the patients of Makkas (151). The ay radiate to the lower abdomen or the left iliac fossa: this occurred f Wright's 435 patients. Radiation to the back occurred in only Wright's cases. The pain is seldom continuous in type (142).

Table 119

SHOWING TIME OF ONSET OF ANASTOMOTIC ULCER AFTER THE OPERATION

Author	*No. Cases*	*Time After Operation*												
		0 to 6 mo.	*6 mo. to 1 yr.*	*1 to 2 yrs.*	*2 to 3 yrs.*	*3 to 4 yrs.*	*4 to 5 yrs.*	*5 to 10 yrs.*	*10 + yrs.*	*0 to 1 yr.*	*0 to 2 yrs.*	*1 to 5 yrs.*	*1 to 10 + yrs.*	*Longest Period yrs.*
Wright, 1935 (142)	429	148	70	66	36	30	17	47	15	218	284	149	196	8
Judd & Hoerner, 1935 (143)	516	199	73	90	37	28	15	62	12	272	362	170	232	
Total	945	347	143	156	73	58	32	109	27	490	646	319	428	
Percentage		37	15	16	8	6	3	12	3	52	69	33	45	
Paterson, 1909 (139)	49	18	11	8						29	37		29	8
Jones, 1928 (140)	37			13						17			29	17
Benedict, 1933 (141)	35	5	2	2	8	5	2	8	3	7	9	17	28	18
Marshall & Devine, 1941 (144)	47	21	5					6	5	26		10	21	
Ginzburg & Mage, 1938 (146)	86									36			36	19
Baltscheffsky, 1943 (147)	33			3	7	3	1	6	3	10	13	11	23	20
Total	1232	391								619	705	337	590	
Cases reported		1076								1232	1062	1060	1232	
Percentage		37								50	70	34	50	
Mage* 1942 (145)	40			11	6					15	24	21	27	17

The pain is related to the intake of food. The pain occurred after meals in 74 per cent of Wright's cases. In 15 per cent, the pain started within 30 minutes after eating; in another 15 per cent, one half to one hour afterward; in 24 per cent, between one and two hours afterward; and in 20 per cent, more than two hours afterward. The taking of food gives some relief to from 80 to 95 per cent of patients. Alkalies with or without milk or bland food provide some relief in most cases, as is true of peptic ulcer in general.

Night pain occurs in from 33 to 50 per cent of patients with anastomotic ulcer (152–154).

The sudden onset or exacerbation of pain frequently indicates a perforation. It is apparently quite uncommon for perforation to occur as the first sign of an anastomotic ulcer. The literature is too meager to warrant the citation of a percentage.

Hemorrhage. Manifest hemorrhage occurs in 35 per cent of patients with anastomotic ulcer (Table 83, p. 595). Painless bleeding occurs in about 12 per cent of patients (140, 153, 155). Mage (155) has suggested that painless bleeding arises from a superficial erosion or ulcer, whereas bleeding with pain indicates a penetrating lesion.

Vomiting. Vomiting occurred in 60 per cent of 386 cases of anastomotic ulcer collected by Wright (142), as in 60 per cent of 79 cases reported by Walton (149). In smaller series of cases reported by others, vomiting occurred in from 10 to 36 per cent of the patients. It must be remembered that vomiting may occur in a malfunctioning stoma and a gastrojejunocolic fistula. However, an anastomotic ulcer was found in 77 per cent of 62 surgical specimens from patients operated on for a malfunctioning stoma (156). The vomiting may be fecal in some cases of gastrojejunocolic fistula (142).

Loss of Weight. This occurs in approximately one half of the patients (142, 153). Wasting may occur in gastrojejunocolic fistula.

Diarrhea. This is not a common symptom of uncomplicated anastomotic ulcer. It is a common symptom of a rapidly emptying stomach and of a gastrojejunocolic fistula.

Physical Examination

In the presence of an anastomotic ulcer, a palpable mass is more frequently found in association with an anterior gastroenterostomy (32 per cent) than with a posterior one (3 per cent) (142). Tenderness on pressure at the level of the umbilicus is usually present. In 340 patients, it was in the midline in 157, to the left in 85, to the right in 26, and in the left iliac fossa in four; tenderness was absent in 68 (142). Some rigidity is usually associated with the tenderness.

Laboratory Examination

Gastric Analysis. A fasting specimen may occasionally contain acid (157) and the results of a single test-meal may suggest the prese of achlorhydria (140, 142, 152, 158). However, there are no cases anastomotic ulcer on record in which repeated analyses and the use histamine established the presence of a true achlorhydria. In most ca when the tube is not in the jejunum, a normal or high acidity is fou None of 436 patients on whom a gastroenterostomy for gastric cancer h been performed developed an anastomotic ulcer (142). This is of inte because of the high percentage of achlorhydria found in gastric can patients.

Anemia. Anemia, which may be due to bleeding, a "dumping sto ach," or a gastrojejunocolic fistula, is rather frequently found. Jones (1 found occult blood in 84 per cent of 42 patients and Linn (153) in 90 cent of 11 cases. A stool examination shows considerable wastage of f in patients with a "dumping stomach" or gastrojejunocolic fistula.

Roentgenologic Examination

The crater of a jejunal ulcer was apparently first demonstrated Barsony (159). At about the same time, Carman and Balfour (1 expressed the view that roentgenologic examination could usually go further than indicating the presence or absence of a pathologic pro about the stoma. Soon after, the technique improved so that Ström (1 in 1923 found a crater in five patients, the existence of which was pro on the three subjected to operation. Camp found craters in a series of ei patients, in five of whom the diagnosis was confirmed by operation. expressed the opinion that craters could be detected in 60 per cen patients with an active anastomotic ulcer (162, 163). Wright (142), in collected series, found that a crater had been recognized in only 13 cent of 183 patients in whom the x-ray examination was considered t positive for jejunal ulcer.

The visualization of a crater is obviously necessary for the abso diagnosis of an ulcer, though marked deformity and occlusion of stoma are highly presumptive signs. Tenderness of the stoma, ga retention, spasticity of the stomach or jejunum, and dilation of stomach or duodenum are the indirect signs of an anastomotic ulcer.

The literature on the accuracy of the x-ray diagnosis in surgic proven cases of anastomotic ulcer, like that of duodenal and gastric u is not extensive. In Wright's (142) collected series, all of which were proven by operation, the error (negative report) was 22 per cent in

ients and doubtful in an additional 10 per cent. In 41 proven cases orted by Ginsburg and Mage (146), the error (negative reports) was per cent. There are a number of reports giving the diagnostic error and e of detection of craters in series of cases which are too small to be aningful (164–166).

Roentgenologic and Gastroscopic Methods Combined

Relatively little work has been reported regarding the results of the nbined use of the roentgenologic and gastroscopic methods of examina-n. Benedict (58, 59), using both methods on 10 gastroenterostomized ients, came to the wrong diagnosis in two. Renshaw (57) used both thods on 43 proven cases of anastomotic ulcer with an error of 19 per t. Gastroscopy improved the diagnosis in 14 per cent of the 43 cases. usgaard (152) and Cooper (167) believe that gastroscopy increases the centage of absolute diagnosis of anastomotic ulcer. The data available stantiate such a view (168, 169, 170).

Late Complications of Anastomotic Ulcer Other than Hemorrhage and Perforation

Stenosis or Obstruction of the Gastroenterostomy Stoma. proximately 10 per cent of anastomotic ulcers produce an organic nosis of the stoma (Table 120). Some jejunal ulcers cause a functional

Table 120

Anastomotic Ulcer Causing Stenosis of Gastroenteric Stoma

Author	*Number of Cases of Anastomotic Ulcer*	*Number with Stenosis*	*Percentage with Stenosis*
d & Hoerner (143)	597	approx. 60	10
se (154)	30	12	40
doni (171)	52	6	12
edict (141)	36	2	6
otal	715	80	11

nosis, which frequently disappears on medical management. There are er causes of obstruction of the stoma, such as the prolapse of redundant cosa into the efferent loop, development of a connective tissue spur with jection into the orifice of the proximal or distal opening of the jejunal tion of the stoma, and technical error of a surgical nature which causes

Table 121

GASTROJEJUNOCOLIC FISTULA AS A COMPLICATION OF ANASTOMOTIC ULCER*

Author	*No. of Anast. Ulcers*	*Source of Material*	*No. of Gastrojejunocolic Fistulas*	*Per Cent Gastrojejunocolic Fistulas*	*Time from Primary Operation*	*Previous Operation Anterior or Poster*
Paterson (139)	72	Proved & Suspected	5	8	..	..
Verbrugge (175)	..	Surgical	19†	..	9 mos. 5 yrs.	..
Jones (140)	42	Proved & Suspected	2	5	..	..
Hurst & Stewart (33)	22	Autopsy	7	34	..	All Posterior
Jacobvici (176)	20	Surgical	3	15	..	..
Valdoni (171)	52	Surgical	5	10	..	..
Benedict (141)	36	Proved & Suspected	5	14	..	..
Graham & Lewis (177)	43	Proved & Suspected	4	9	..	..
Judd & Hoerner (143)	597	Surgical	52	9	Average of 5.7 yrs.	..
Lahey & Swinton (178)	30	Proved & Suspected	9	27	..	..
Wright (142)	458	Proved & Suspected	40	9	..	Two of a Total Cases Followe terior Polya tomosis
Emery & Monroe (309)	47	Surgical	7	13	..	..
Grossman (179)	23	Surgical	2	9	..	Both Posterior
Finsterer (180)	226	Surgical	19	8	..	..
Walters & Clagett (184)	..	..	50†	..	Average of 45 mos.	..
Lawson (181)	21	Proved & Suspected	3	14	..	..
Rienhoff (183)	23	Proved & Suspected	0	0	..	All Anterior tions
Ransom (310)	..	..	18†	..	1–26 yrs. Average 9½ yrs.	Post. Gastro-enterostomy
Bruusgaard (152)	70	Proved & Suspected	5	7	.	..
Klingenstein (182)	44	..	8	18	2–30 yrs.	Post. Gastro-enterostomy
Total	1826	..	176	9.6		

* Ivy and Fainer (173).

† Not included in totals.

ction on the anastomosis or herniation of a loop of jejunum into the er peritoneal sac. These are much less common than the first two ises of obstruction at the stoma. The stenosis is generally due to an astomotic ulcer (156, 171, 172).

Symptoms. The symptoms are vomiting and loss of weight without or h the jejunal ulcer type of pain. A previous history of jejunal ulcer is ally obtained, followed by more acute distress, bloating, belching and ness after eating, nausea and vomiting, and loss of weight and appetite. Roentgenologically, gastric retention and dilation and delayed tric emptying are found. It is well to note that vomiting occurs in re than 40 per cent of patients with anastomotic ulcer (p. 781) and is erally more frequent in anastomotic than in duodenal ulcer.

Gastrojejunocolic Fistula. *Past History.* Approximately 10 per cent patients with an anastomotic ulcer develop a gastrojejunocolic fistula able 121). The time interval between the performance of the gastro-nostomy and the development of the fistula is obviously related to the e interval for the development of the anastomotic ulcer, which per-ates into the colon. In the 1,826 cases collected in Table 121, the aver- time of the diagnosis of the fistula after the gastrojejunostomy was proximately five years, the range being from nine months to 30 years. anatomic reasons, almost every case of gastrojejunocolic fistula occurs r a posterior gastroenterostomy. The complication is limited almost rely to males because they are more susceptible to anastomotic ulcer its perforation.

Symptoms. The symptoms of gastrojejunocolic fistula are diarrhea, iting, and loss of weight with or without the disappearance of pain or horrhage due to the anastomotic ulcer. One or more of these symptoms y be absent. In the 40 cases collected by Wright (142), *diarrhea* was sent in 85 per cent, being severe in only 45 per cent; *vomiting* was sent in 90 per cent, being fecal in 27 per cent and severe in 25 per cent; *of weight* or wasting occurred in 75 per cent and was severe in 30 per t; and *pain* was present in one half of the cases but severe in only 10 per t. The onset of a gastrojejunocolic fistula is quite frequently charac-ized by disappearance of pain and appearance of diarrhea.

Roentgenologic Examination. Gastrojejunocolic fistula has to be erentiated principally from the similar symptom complex which urs in the rapidly emptying or "dumping" stomach and from various causes of a chronic diarrhea. The diagnosis of fistula cannot made with certainty until it has been demonstrated roentgenolog-ly. This is done more readily by the use of a barium enema than a barium meal (174).

Differential Diagnosis of Peptic Ulcer and Functional Dyspepsia

Introduction

It is foreign to the purpose of this book to discuss thoroughly the subject of the dyspepsias. The subject must be considered in a restricted manner, however, because the dyspepsia of peptic ulcer must frequently be differentiated from dyspepsia due to other causes (32, 38).

Definition

Dyspepsia and indigestion are very general terms referring to symptoms referable to disturbances of the gastrointestinal tract. For example, Rush (186) reports that 200 patients were admitted to a large city hospital under the diagnosis of "dyspepsia." Eighty per cent of these patients were found to have a *spastic or irritable colon* which was activated by coarse foods. These patients were classified as having "dyspepsia" only because they had abdominal cramps soon after eating.

The expression "dyspepsia" will be used by us to refer to a group of symptoms which suggest to the physician that the stomach and duodenum may be functioning abnormally. For clearness, four general types of dyspepsia will be mentioned before considering "functional dyspepsia."

Classification of Dyspepsias

Dyspepsia Due to Organic Disease of the Stomach, Duodenum or Esophagus. This includes the congenital or acquired abnormalities, diaphragmatic hernia, chronic duodenal obstruction, and allergic reactions.

Dyspepsia Due to Reflexly Initiated Disturbance of the Stomach or Duodenum. This is secondary to organic or functional disease of the appendix, colon, gallbladder, bile ducts, pancreas, intestine, genitourinary tract, and epigastric hernia. Acute organic or functional diseases of the organs just mentioned also produce symptoms which are quite characteristic and are usually quite readily differentiated from disturbances of the stomach and ulcer-bearing portion of the duodenum: for example, appendiceal colic, colon colic or cramps, gallstone colic, and renal colic.

Dyspepsia Due to Systemic Disease. Included are toxemias, disturbances of metabolism and of the glands of internal secretion (hyperglycemia) and the nutritional deficiencies.

Dyspepsia Due to Functional Gastric and Duodenal Disturbances. These disturbances are not secondary to detectable organic or functional disease outside the stomach or duodenum.

Incidence of the Four Types of Dyspepsia

ecent information on the relative incidence of the four types of psia is not available. Data available prior to 1930 indicated that the nce due (1) to local organic disease such as peptic ulcer was 11 to r cent, (2) to reflex disturbance was 30 to 40 per cent, (3) to systemic se was 16 to 20 per cent, and (4) to functional causes was 22 to 25 per (38).

uring the recent war, among the personnel of the armed services of nited States and Great Britain (187), the incidence of the diagnosis spepsia due to peptic ulcer and the incidence of the diagnosis of tional dyspepsia" were approximately equal in 13,000 patients ted from the literature by Friedman (188). The ratio of the inci- of peptic ulcer to functional dyspepsia ranged from 90 PU:10 FD PU:75 FD in the various reports that Friedman collected.

hese data from the recent war cannot be applied to the civilian lation, which includes all age groups and an approximately equal on of males and females. In the civilian population, dyspepsia due lex and systemic causes and to gastric cancer will be more common.

Functional Dyspepsia

here are probably two types of "functional dyspepsia." "Probably" d because the exact role which gastritis, an organic disease, plays e symptomatic picture is uncertain. The first type that we shall nize and discuss is "dietary or habit dyspepsia"; the second type is honeurotic dyspepsia" with or without an associated gastritis.

IETARY DYSPEPSIA OR HABIT DYSPEPSIA. Eusterman and Balfour (38) he expression "habit dyspepsia" because the condition is attributed patient's unhygienic habits of living as well as eating.

he patient complains of "acid indigestion," or "sour stomach," or dyspepsia" because he has acid eructations with or without belching eating. There is frequently no epigastric distress, though burning or ating sensation may be felt. Alkaline powders usually give relief. times the patient complains of a "sensitive stomach" with or without dyspepsia," the chief symptom being nausea and vomiting after .

he history usually reveals that the patient eats and sleeps irregularly ts too fast and heartily of heavily seasoned and rich foods. This is imes associated with excessive smoking or excessive drinking of olic or caffeinated beverages. In some persons, "overeating" for l days will produce the same symptoms; in others, "overeating" for r two meals, as on Thanksgiving, will cause symptoms lasting several

days. The regular taking of moderate sized meals of a bland, smooth for a few days during the search for an organic cause will often resu the disappearance of the symptoms. Frequently, the patient will volun such information when the history is being taken.

Tidy (187) speaks of a "transient dyspepsia" which occurred in soldi while they were being hardened to army life. He points out that impro handling may convert them into "chronic dyspeptics." A group of tients of this description where a "tension state" is not involved have been studied to find how frequently gastritis is present. If presen would be expected to involve principally the pyloric portion of stomach, because these patients have a normal or hypernormal acidi the gastric contents.

The dietary type of dyspepsia is called functional only tentati because it may be found to be due to gastritis or duodenitis in some c and to a reflex disturbance from some other part of the alimentary in others.

Psychoneurotic Dyspepsia with or without Gastritis. Other t used are "gastric neurosis," "dyspepsia of chronic nervous exhausti "nervous indigestion," "chronic non-ulcerative dyspepsia," "dyspep the constitutionally inadequate," and "functional dyspepsia." Under heading, we do not include such acute conditions as nausea and vom with or without epigastric pain following more or less acute emot embarrassment and such a chronic condition as anorexia nervosa. (I student of this problem is referred to Alvarez's book, "Nervous Indigestion, and Pain" (189).)

Analysis of Problem. The most complete evidence bearing on existence and diagnosis of psychoneurotic dyspepsia is to be foun several articles dealing with studies in which soldiers during the r war were the patients. These soldiers were examined gastroscopically psychiatrically as well as by the usual methods. Though the percen may be different for a civilian group, the principles revealed by the on soldiers should apply to a civilian group.

In actual practice, after attempting to rule out the first three gr causes of dyspepsia, one is left with a group of patients who have ch epigastric distress or symptoms referable to the esophagus, stomac duodenum due to some cause not revealed by the ordinary roentgeno laboratory, and clinical examinations. These patients are either mar under the diagnosis of functional or psychoneurotic dyspepsia o subjected to a gastroscopic and psychiatric examination.

Table 122 presents the findings on 169 patients collected from fi which give complete gastroscopic and psychiatric data. *First*, it sho noted that nine of the 169 patients had neither gastritis nor psychon

DISTRIBUTION OF PATIENTS "WITHOUT" A DETECTABLE ORGANIC CAUSE OF THE CHRONIC DYSPEPSIA, EXCLUDING PSYCHIATRIC AND GASTROSCOPIC EXAMINATION

Author	*Total No. Cases*	*With Neurosis*						*Without Neurosis*						*Total with Gastritis*	
		Totals		*With Gastritis*		*Without Gastritis*		*Totals*		*With Gastritis*		*Without Gastritis*			
		No. Cases	*Per Cent*	*No. Cases*	*Per Cent*	*No. Cases*	*Per Cent*	*No. Cases*	*Per Cent*	*No. Cases*	*Per Cent*	*No. Cases*	*Per Cent*	*No. Cases*	*Per Cent*
Halsted et al. (190)	110*	93	84.5	34	36.5	59	63.5	17	15.5	11	65	6	35.0	45	40.8
Montgomery et al. (191)	22	17	77.3	8	47.0	9	53.0	5	22.7	3	60	2	40.0	11	50.0
Schwartz et al. (192)	37†	30	81.0	12	40.0	18	60.0	7	9.0	6	86	1	14.0	18	47.0
Total	169‡	140	82.8	54	38.5	86	61.5	29	17.2	20	70	9	30.0	74	43.8

* Condition started before Army life in 87 per cent and there was a family history in 56 per cent.

† 3 of these cases had duodenal ulcer and no gastritis.

‡ 9 of 169 patients or 5.0 per cent had neither gastritis nor neurosis.
20 of 169 patients or 12.0 per cent had gastritis but no neurosis.
54 of 169 patients or 33.0 per cent had neurosis *with* an associated gastritis.
86 or 169 patients or 50.0 per cent had neurosis *without* an associated gastritis.

to account for their symptoms of chronic dyspepsia. These patie
have had a hidden ulcer (see Errors in Diagnosis, p. 787), or sy
from intestinal parasites, from a hidden lesion in some other viscus
a reflex or systemic disturbance of the stomach, or some of them m
been successful malingerers, which is unlikely. *This yields an "e*
5 per cent in the diagnosis, the "error" being that the symptoms ca
accounted for.

Second, it should be noted (Table 122) that approximately 80 p
of the 169 patients had a psychoneurosis or a "tension state" a
40 per cent of these psychoneurotics had a gastritis. *Thus, the*
could have caused the symptoms in only 40 per cent of the psychoneuro

Third, about 20 per cent of the 169 patients did not have a
neurosis and 70 per cent of these 20 per cent had a gastritis. *Thus,*
cent of the 169 patients, gastritis was the only possible cause of the symp
covered. Either gastritis was the cause of the symptoms or the total
omission in this group of 169 patients was 17 per cent (5 per
12 per cent).

The findings in the 169 patients may be classified as follows:
of omission, or failure to find a cause of the symptoms, in 5 per c
gastritic dyspepsia, which would classify these patients as a dysp
Type A, in 12 per cent; (3) "*psychoneurotic*" *dyspepsia with gastritis* i
cent; (4) "*psychoneurotic*" *dyspepsia without gastritis* in 50 per cent.

These data strongly indicate that superficial gastritis alone ma
symptoms of chronic dyspepsia in some patients. Although it is wel
that gastritis may be present without causing symptoms, there i
reason to believe that gastritis associated with a tender silhouet
stomach should cause symptoms.

The data also strongly indicate that psychoneurosis may be th
of dyspepsia, there being no doubt regarding the fact that psycho
may result in symptoms of dyspepsia. The suggestion that gastr
be the cause of a psychoneurosis (193) is not applicable to 80 per
the psychoneurotic patients, since they did not have a gastritis. M
in some patients, the symptoms may abate under treatment for
neurosis without there being a change in the appearance of the
and edematous gastric mucosa (190). Nevertheless, in the pres
stomach tender to pressure, it is reasonable to assume that gastri
contribute to the symptoms in a psychoneurotic patient.

Because it has been well known since the time of Beaumont
[751] that emotional states may cause congestion of the gastric m
changes like those described for superficial gastritis, it is possible
emotional state caused the gastritis observed. It is also possible, s
patients (85 per cent) with psychoneurotic dyspepsia report that th

ceen present for years, that many repetitions of the congestion
organic changes found in frank cases of "chronic superficial
It is odd that such patients do not develop peptic ulcer, if a
state" is a primary etiologic factor.

ymptoms in "psychoneurotic dyspepsia without gastritis" must
imaginary. If real, they may be due to abnormalities in gastric
nd secretion, or to an exaggerated or abnormal interpretation
gastric sensations which everyone experiences.

ms. The *pain or distress* in the epigastrium is described as discom-
ling of fullness or pressure, or aching, or burning, or fluttering,
sharply localized as a rule. The discomfort occurs character-
ithin the first half hour after eating, usually within a few minutes.
two thirds of the patients, it occurs once or twice a day regularly
g; in others it is unpredictable (188). The ulcer patient usually
ore clear-cut pain history. *All authors agree that alkalies usually
istress and food usually does not* (188, 192, 197, 198). For example,
nd Copeman (198) found that food relieved 72 per cent of ulcer
43 per cent of non-ulcer dyspepsia; alkalies relieved 77 per cent
nd 62 per cent of non-ulcer dyspepsia. *Nausea and vomiting* occur
; this symptom occurred in 50 per cent of Friedman's non-ulcer
nd in only 5 per cent of his ulcer ones. On closer questioning, the
" may frequently be found to be regurgitation only (190), but
hat nausea and vomiting are more frequent in psychoneurotic
ic ulcer dyspepsia. *Bloating, belching, and aerophagia* are other
ymptoms. Except for a variable amount of insomnia, there are
at night.

patients, in contrast to most ulcer patients, have a multiplicity
ms. Notable among these are headache, weakness, easy fatiga-
rheadedness, dizziness, lassitude, anorexia, insomnia, palpita-
in the chest, inability to relax, hyperirritability, and food
cies. They are concerned about their symptoms and desire to
ganic cause for them. About 85 per cent of patients have had the
for several years and a family history of a similar disorder may
n 56 per cent (190).

e to Ulcer Therapy. These patients as a rule do not respond well to
agement (38, 188, 190, 197). They respond best to a sedative
dium amytal.

eurosis or Neurotic Traits. The incidence of psychoneurosis or
idence of neurotic traits range from 8.5 to 17 per cent in ulcer
nd from 18 to 85 per cent in patients with "functional dyspepsia"
191, 199, 200). The variation is apparently due to the criteria
y about half of the patients with functional dyspepsia and

neurotic traits are actually classified as definitely psychoneur neurasthenic or constitutionally inadequate by most authors.

Physical Examination. The physical examination reveals th of the patients have a generalized tenderness in the epigastrium, larly over the silhouette of the stomach. The tenderness is not loca in peptic ulcer. There is no statistically significant evidence show body habitus is related to functional dyspepsia. *Functional dysp civilian life, is reported to be more frequent in the female* (201), *which is to peptic ulcer.*

Laboratory Examination. Nothing characteristic is reve gastric analysis and occult blood is absent from the stools. The acid test (p. 786) is reported to be helpful in differentiating fu from ulcer dyspepsia (188, 191). For example, Friedman (188) pain in all of 33 patients with ulcer and no pain in all of 42 patie functional dyspepsia. Pain may occur on distention of the stoma any liquid, whether it be a solution of hydrochloric acid or sodiu bonate. This is not to be taken as a positive acid test, however.

Roentgenologic Examination. No ulcer is found, though an duodenum is sometimes reported. Occasionally hypertrophic ga observed (190).

Gastroscopic Examination. All authors agree that when g present, superficial gastritis (reddening and edema of the muc exudation in some cases) is found in most cases. Hypertrophic when observed, is associated with an ulcerlike type of distress.

Clinically, the patient with psychoneurotic dyspepsia is char by the vagueness and multiplicity of complaints and symptoms. neurotic traits or definite psychoneurosis, and relatively little or from ulcer management.

Other Conditions Which May Be Confused with Pe Ulcer

These conditions will only be listed.

Conditions Intrinsic to the Alimentary Tract. Included disease of the esophagus, such as esophagitis, esophageal tu cardiospasm; (2) diseases of the stomach, such as gastritis, t dyspepsia, benign and malignant gastric tumor, hypertroph pyloric muscle, stenosis of the pylorus, hourglass stomach, diver the stomach, gastric syphilis, gastric tuberculosis, and gastric cri dorsalis; (3) diseases of the duodenum, such as duodenitis, b malignant tumors, duodenal diverticulum, duodenal stenosis, a duodenal ileus or obstruction; (4) diseases of the intestine, such obstruction due to adhesions or tumors, regional ileitis, and

iculum; (5) appendicitis; and (6) diseases of the colon, such as tive conditions, tumors, and functional disturbances.

ONDITIONS OF OTHER VISCERA. These conditions include: (1) coronary bosis or angina and cardiac decompensation; (2) chronic pulmonary e (tuberculosis); (3) diaphragmatic hernia; (4) epigastric hernia; ancreatic diseases (calculi, pancreatitis, tumor); (6) gallbladder e (tumor of the ampulla of vater); and (7) pyelitis, cystitis, and renal i.

STEMIC AND METABOLIC DISORDERS. These are allergic reactions in omach, hyperinsulism, and excessive use of tobacco. See also the of dyspepsia (p. 814) and the causes of gastrointestinal hemorrhage 9).

yloric Obstruction or Stenosis and Gastric Retention

FINITION. Retention of gastric contents may be due to pyloric ob- on or to a functional (nervous, febrile) disturbance in the absence tric or duodenal disease. An obstruction at the pylorus may be due eflex (nervous) spasm, as from an irritated gallbladder, to a hyper- ed pyloric sphincter, to a tumor in proximity to the pyloric orifice, local spasm or inflammation caused by an ulcer in the pyloric canal he duodenal or prepyloric region. The narrowing of the pyloric canal e functional (reflex) or organic (inflammation or scar tissue). d of the sphincter being in spasm, it may simply not relax normally reflex disturbances, a condition referred to as achalasia of the sphincter. Narrowing of the duodenal bulb by spasm or scar may ause retention.

MPTOMS. In cases of mild retention, there may be no symptoms.

igastric Distress. In severe cases, a feeling of distention or bloating r without continuous or intermittent pain is experienced. The s is characteristically relieved by vomiting or aspiration. Some ts relieve themselves by stimulating the pharynx with their finger. ients hyposensitive to visceral pain, the symptoms of peptic ulcer ave disappeared or may have never been present, so that the first oms of ulcer disease may be those of distention relieved only by ng. If hyperperistalsis is marked, intermittent cramplike pain is felt. g standing cases of organic stenosis, the peristaltic activity of the ch is slight and only distention is present. The vomitus contains food ix or more hours before. If high-grade obstruction has been present ne time, the patient will also complain of weakness and loss of .

YSICAL EXAMINATION. If the patient has a thin abdominal wall, peristalsis may be seen when the stomach is distended with food and

the patient is having intermittent distress. Visible peristalsis can be duced in the patient with an empty or almost empty stomach by g half a glass of water containing a teaspoonful of sodium bicarbonate. is followed by a half glass of water containing a teaspoonful of tar acid, which is taken slowly while the abdomen is being examined. Th the normal stomach may be outlined by this method when the abdor wall is thin, the occurrence of readily visible peristaltic waves is str presumptive of pyloric obstruction. Reverse peristalsis may be particularly if the patient has obstruction and is nauseated. A *succ splash* in the region of the epigastrium may be heard on shaking the Emaciation and dehydration are evident in some patients with standing high-grade obstruction.

Laboratory Examination. If the early morning gastric residu found to contain food eaten the previous day, it is strongly presum that high-grade obstruction is present. The same is true if sarcinae or are present in the residuum.

Some use the "motor meal" to obtain an idea of the extent o obstruction. It consists of 100 Gm. each of boiled potato, spinach, ca and raw apple, one egg, one slice of bread with one pat of butter, 1 of dry tea leaves, and beverage as desired. This is taken when the sto is empty and nothing else is taken. The stomach is aspirated wit (large) Ewald tube seven hours after eating the meal. The normal sto unless there is fever, nausea, headache, or an emotional disturb should yield no more than 60 cc. of liquid with a few tea leaves. Th stomach is washed with four bulbfulls of tepid water. After the first b is aspirated, the remainder should return clear.

The "pyloric balance test" is performed by evacuating the st and introducing 200 cc. of water or protein hydrolysate. In two hou stomach is again evacuated. The presence of 200 cc. or more in high-grade obstruction, 200 to 60 cc. moderate or partial obstructio 60 cc. or less normal emptying.

Roentgenologic Examination. Abnormal retention of the b meal is observed. At times a 24 or even 36 hour residue of barium is This is the most accurate way to determine the degree of retention

Therapeutic Diagnosis of Functional Versus Organic Rete Gastric retention has approximately the same incidence in gastr duodenal ulcer, though it tends to occur more frequently with the f It occurs in from 25 to 30 per cent of cases (38). In one third of th of gastric ulcer with retention, the ulcer is remote from the pyloric This indicates that the retention is due to pylorospasm, since the activity is normal or hypernormal in these cases (38).

Berkman (202) has found that when patients having retenti

rated upon, the retention can be ascribed to organic stenosis in only roximately 20 per cent of gastric ulcer and 8 per cent of duodenal ulcer ients. (Gastric retention occurs in about 40 per cent of patients with tric cancer (38)). One, then, may expect the gastric retention to dis- ear completely or to a large extent in 80 per cent of the patients with tric ulcer and in 92 per cent of the patients with duodenal ulcer on ctive therapeutic management.

The extent of the relief of the retention in consequence of therapy is followed by *roentgenographic study*. As the therapy is followed, the ntion becomes less. In some cases in which it is due to reflex pyloro- sm or to local inflammation, it may disappear in from three to 14 days. ases where the retention is due to a combination of spasm, inflamma- , and scar, only a portion of the retention will disappear during a od of from two weeks to three months.

Using the fluoroscope, retention due to spasm may be seen to disappear bserving the diameter of the pyloric canal when barium is passing ugh it. In the case of duodenal deformity, the irritable spastic bulb, d by irregular action of the pylorus and bulb, will respond to strict nagement in several days to two weeks. If the narrowing is due to scar, ill persist for weeks and months and its maximum width can be meas- l under fluoroscopic examination. The width of the normal bulb is 2 3 cm. When the deformed bulb at its narrow point measures 5 to nm., the stenosis is moderate and when 2 to 4 mm., it is marked. When narrow point is 1 mm. in width, then gastric dilatation is usually found ballooning of the antrum and hyperperistalsis (203). On manage- t, an increase in the width of the narrow point may be seen up to six ths after starting management.

Alkalosis. Occasionally the patient with pyloric obstruction vomits a t deal and loses so much HCl that alkalosis develops along with ydration and produces the following symptoms and signs: nervous ability, flushed face, anxious expression, paresthesia, and headache; in severe cases, semistupor and twitching of facial muscles and fingers contracture or the actual convulsions of "gastric tetany." The ostek and Trousseau signs are present.

Hypertrophic Pyloric Stenosis. Hypertrophy of the pyloric sphinc- nay be found in adults in association with a gastric ulcer. It may occur out gastric ulcer. When it occurs with ulcer, it may be only a con- itant lesion or the retention may have served as an excitatory cause he formation of the ulcer. It is usually not possible to ascertain ther the hypertrophy arose in the adult or has been present since ncy. Vomiting is the chief symptom and nausea may be marked. Pain istress when present is mild. Large meals are not tolerated (204).

Hourglass Stomach

This is diagnosed by roentgenologic examination. The distress is mild when present and vomiting may occur or be induced by the patient. In some cases, the hourglass effect is due to a persistent circular spasm rather than a scar and will disappear under medical therapy for the peptic ulcer which is always located on the lesser curvature opposite the indentation on the greater curvature. The hourglass effect may be due to cicatricial contracture plus spasm. That is, there may be a scar from a partially healed "saddle ulcer." The spasm usually disappears when the ulcer heals under medical therapy.

Perforated Peptic Ulcer

Introduction

There are two general types of perforated peptic ulcer. The first may be referred to as a "major acute perforation of the acute surgical type." The second may be referred to as a "minor acute perforation with early spontaneous closure." Sometimes the perforation is such that a pocket is locally formed at the site of the perforation, which air or barium may enter, or which may become a diverticulum or an abscess.

Major Acute Perforation of the Acute Surgical Type

Three stages of the disease caused by this complication of peptic ulcer are recognized. These are: the *first stage* or dramatic stage, due to the irritation of the peritoneum with gastric and duodenal contents; the *second stage* or stage of delusion, in which the condition of the patient appears to improve; and the *third stage*, in which the symptoms of a generalized or localized peritonitis are evident.

First Stage

History. The most significant point in the history of a patient with a perforated ulcer is the history of peptic ulcer. However, it was not elicited in 14.8 per cent of 6,110 cases of perforated ulcer (205).

Symptoms. *Pain.* The most common complaint is pain. It occurred in 79.1 per cent of 2,132 patients with perforation (205). Though generally sudden in onset, it may gradually become more severe. It is variously described as agonizing, intolerable, tearing, bursting, knifelike, stabbing, or intense. It is generally constant with intermittent exacerbations. In 2,132 patients, it was felt most severely in the epigastrium in 64.1 per cent, throughout the abdomen in 15.0 per cent, in the right lower quadrant in 4.9 per cent, in the right upper quadrant in 2.8 per cent, in the left upper quadrant in 0.3 per cent, and in the back in 1.6 per cent. *Shoulder pain* or

supraclavicular pain was present in 22.6 per cent of 2,132 patients (205). When looked for, it may occur in 60 per cent of cases (206). Pain in the shoulder is due to irritation of the central portion of the diaphragm; the shoulder pain generally involves the right shoulder.

Prostration. When the pain is severe, the patient is prostrated. The face is pale and has an anxious expression; the mouth is tightly closed; and respiration is rapid, shallow, and costal in type. The skin tends to be cold and clammy and the body is held rigid. This is frequently called "shock." As a general rule, however, the blood pressure is not low, and the term "shock" cannot be used in the sense that it is in the expression surgical or traumatic shock. In 364 cases of perforated ulcer, the blood pressure was normal in 80 per cent (208). Shock does occur in some patients, and a systolic blood pressure below 100 is a grave sign (209).

Nausea and Vomiting. The occurrence of nausea and vomiting is quite variable. Various authors report that it occurs with a frequency of from 13 to 96 per cent. The average incidence in 2,190 cases of perforated ulcer was 45.8 per cent (205).

Hemorrhage. Hemorrhage occurred in association with perforation in 6.1 per cent (p. 551) of 2,525 cases (205). It may be recalled that anterior wall ulcers are more likely to perforate and posterior wall or lesser curvature ulcers are more likely to bleed. Although it is generally believed that the combination of hemorrhage and perforation has a graver prognosis than either alone, the data are too few to warrant a definite conclusion.

PHYSICAL FINDINGS. *Abdominal Rigidity and Tenderness.* The most common sign of perforated peptic ulcer is a *boardlike rigidity of the abdomen with tenderness.* It was found in 87.5 per cent of 2,011 patients. The tenderness and rigidity is more marked in the upper abdomen. "False rigidity" due to fear or malingering is evidenced by a momentary relaxation at the end of inspiration (210). Rigidity may be absent or slight in the presence of tabes dorsalis, shock, poor muscular development, or cachexia.

Obliteration of Hepatic Dullness. This is variable since the incidence of its occurrence, according to various authors, ranges from 0 to 100 per cent. In 1,133 cases, it occurred in 49.2 per cent (205). A distended colon may be a cause of loss of liver dullness.

Auscultation of Abdomen. As a rule, auscultation of the abdomen in the presence of peritonitis reveals an absence of bowel sounds. Because of the presence of adynamic ileus in generalized peritonitis, it has been said that the abdomen is as "silent as the grave."

Temperature, Pulse Rate, and Respiration. In the early stage of perforation, the temperature has been found to be normal in 68.6 and the pulse in 74.8 per cent of cases. The respiratory rate was increased in 62.3 per cent and respiration was costal in type (205).

Laboratory Findings. *Leucocytosis.* The leucocyte count has be found to range from 3,800 to 36,500, with 70 per cent of the cases rangi from 10,000 to 18,000.

Roentgenologic Examination. The demonstration of spontane pneumoperitoneum is a reliable and valuable method for diagnosing acute perforation of an abdominal viscus. Though this procedure w suggested by Popper (211) in 1915, its value was not popularized un after Vaughan and Brams (212) published their observations in 1925.

Pneumoperitoneum is not found in all cases of perforation. Accordi to various reports, its occurrence ranges from 50 (213) to 100 per cent. occurred in 69.4 per cent of 1,267 collected cases (205). In one series 374 patients with perforated ulcer, air was found in the peritoneal cav in 77.5 per cent (207). In the upright or sitting position, the gas is usu found between the right leaf of the diaphragm and the liver. As the posit of the patient is changed, the gas bubble assumes the highest level. patients with adhesions, the gas bubble may be trapped locally by adhesions. There is no significant difference in the incidence of the occ rence of pneumoperitoneum in perforation from a gastric or duode ulcer (214).

Attempts have been reported to increase the incidence of the posi diagnosis of pneumoperitoneum in perforated ulcer. Odom and De Ba (215) injected 20 to 30 cc. of air through a tube into the stomach and t placed the patient in the left lateral position for several minutes. Then assuming the sitting position, air was seen between the diaphragm liver. This is recommended only in selected cases.

Every peptic ulcer patient with an acute exacerbation of sympt even though not agonizing, should be examined radiographically pneumoperitoneum, since a "forme fruste" or minor acute type of perf tion may be present. It should also be remembered that spontan pneumoperitoneum may occur from perforations of other portions o alimentary tract such as the appendix, small intestine, and colon.

Sometimes it is not easy to locate the site of perforation at opera this is particularly true of the ulcer which perforates near the esopha into the lesser peritoneal cavity. Baker (216) and others (217, 218) reported that the introduction of 60 or 100 cc. of dilute methylene solution into the stomach is useful.

Subcutaneous emphysema may follow perforation of peptic (219, 220).

Serum or Urinary Amylase. Perforation into the pancreas o presence of an associated pancreatitis is diagnosed by the detection decided increase in serum or urinary amylase (221).

Errors in Diagnosis. The accuracy in the *preoperative* diagno perforated peptic ulcer ranges from 83.5 to 95.3 per cent in dif

orts in the literature. In 2,322 cases collected by De Bakey (205), the rage accuracy was 85.7 per cent.

In the collected series of De Bakey (205), with a total of 14 per cent neous diagnoses, a perforated peptic ulcer was erroneously diagnosed the following diseases: appendicitis, 6.8 per cent; acute cholecystitis, per cent; acute abdomen, 1.0 per cent; intestinal obstruction, 0.8 per t; acute pancreatitis, 0.2 per cent; pneumonia, 0.19 per cent; coronary mbosis, 0.09 per cent; miscellaneous, 3.2 per cent. The confusion with endicitis is ascribed to the tendency of the spilled contents to gravitate he right iliac fossa (222). In rupture of a gastric ulcer at or above the sura angularis or of a perforated jejunal ulcer, the pain is likely to be re intense on the left and the left lower quadrant may be involved. ntents may drain along the colonic gutter to cause a pelvic peritonitis. The following are diseases in the miscellaneous group which must be d out: coronary occlusion, gastric crisis of tabes dorsalis, mesenteric mbosis, intussusception, rupture of a tuberculous or typhoid ulcer, l colic, pneumonia, diaphragmatic pleurisy, ruptured ectopic preg- cy, twisted ovarian cyst, renal colic, and acute alcoholism.

Second Stage ("Stage of Delusion")

In from two to six hours after a perforation, the severity of the pain ds to subside, the skin becomes warmer, and the patient appears less ious. The abdominal rigidity and tenderness and the costal breathing tinue.

Third Stage

Generalized peritonitis is responsible for the clinical picture of the d stage. It usually appears from six to 12 hours after the perforation, it does not always appear and if it fails to do so then it is designated forme fruste type of perforation. The temperature, pulse, and respira- are increased and the abdominal tenderness and rigidity may dimin- Ileus is prominent and singultus (hiccough) frequently occurs.

Minor Acute Perforation with Early Spontaneous Closure

Terms applied to this type of perforation include: "forme fruste" oration; "gedeckte perforation"; "subacute perforation"; and "per- tion fermée et isolée." This type of perforation is ushered in by ptoms of the major acute type, but the disease remains localized and symptoms slowly abate in from two to 10 hours. As a rule, the patient eriences an exacerbation of ulcer symptoms one to three days before ther abrupt onset of severe pain, though the pain is generally not so uciating and the prostration not so great as in the major type of oration. However, the boardlike rigidity may be quite marked for a

few hours, especially in the epigastrium (223, 224). Air is found under the diaphragm in the majority of cases and confirms the diagnosis.

Perforated Anastomotic Ulcer

The clinical manifestations of a perforated anastomotic ulcer do not vary significantly from those of a perforated gastric or duodenal ulcer. The pain is likely to be more intense on the left side and in the left lower quadrant.

Mechanisms of Symptoms and Signs of Perforation

The intense pain is due chiefly, if not entirely, to peritoneal irritation by the digestive juices and intestinal contents. Pass (225) in dogs and Watson (226) in human patients observed pylorospasm in cases of duodenal perforation. The former investigator produced pylorospasm by peritoneal irritation in dogs. Since it is well known that pylorospasm can produce pain when it occurs, it undoubtedly contributes to the pain picture. That it is not solely concerned is shown by the occurrence of typical agonizing pain when an anastomotic ulcer ruptures in patients with a subtotal gastric resection.

It has been found experimentally by Blalock (227) that the injection of the digestive juices alone or in combination into the abdominal cavity of dogs produces a picture of abdominal rigidity and tenderness and prostration similar to that seen in patients with perforated peptic ulcer. Infection obviously is not a cause of the early symptoms (first stage) because the abdominal contents are usually sterile for the first six to 12 hours (205). Bile, which has a cytolytic action due to bile salts, is the most irritating of the individual juices, a combination of bile, pancreatic juice, and food is even more injurious. The very early effects appear before much absorption could occur, so they must be due to irritation. Later, toxic material resulting from irritation and, after six hours, from bacterial action could contribute to the picture. The local irritation also causes local vasodilation and congestion. The blood volume and the cardiac output decreases. The blood pressure usually does not fall to the shock level because of compensatory vasoconstriction of distant vascular beds. However, in extensive or severe involvement, the complete picture of traumatic shock may occur (227).

Hemorrhage from Peptic Ulcer

Introduction

The patient with severe hematemesis or melena presents two paramount diagnostic problems. These are (1) the diagnosis of the cause and

source of the bleeding, and (2) the diagnosis of the gravity of the bleeding. The correct solution of these problems is therapeutically important.

Some form of peptic ulcer is the cause of severe hematemesis and melena in approximately 72 per cent of cases, the range in various reports being approximately from 50 to 90 per cent. Hemorrhage from gastric cancer (10.3 per cent), esophageal varices (4.4 per cent), and gastritis (1.8 per cent) make up an additional 16.5 per cent, and an average of 5.5 per cent go undiagnosed. This accounts for 94 per cent, the remaining 6 per cent being due to relatively rare conditions.

In one group of undiagnosed cases, an autopsy or a laparotomy may fail to reveal the source of the hemorrhage (228, 229). Others may represent cases of acute gastritis or of small ulcers which are not detected by roentgenographic study and heal rapidly on medical management.

It is well to point out that hematemesis may be the first symptom in 15 per cent of cases of peptic ulcer, and in 10 per cent of cases of cirrhosis of the liver (235). Hematemesis is rarely the first symptom in gastric cancer. It is not known how often it is the first symptom in gastritis. At any rate, the percentages show that hematemesis without a previous history of a disease predisposing to the symptom is most likely due to a peptic ulcer.

It is not within the scope of this book to discuss the diagnosis of gastric carcinoma, cirrhosis of the liver, gastritis, and the other more rare causes of hematemesis and melena. Appropriate clinical and laboratory examinations will, in almost all cases, indicate the presence of these conditions. The conditions are: duodenitis; Curling's ulcer; benign tumors; syphilis or tuberculosis of the stomach; postoperative hemorrhage; rupture of sclerotic blood vessel; gastric crises of tabes dorsalis; diaphragmatic hernia; trauma; peptic ulcer of the newborn; portal or mesenteric venous thrombosis or portal hypertension; splenic anemia and other types of splenomegaly; diseases of the esophagus such as malignant and benign tumors, peptic ulcer, and esophagitis; syphilis, tuberculosis, and actinomycosis; diverticula and foreign body; blood diseases; jaundice with prothrombin deficiency; diseases of adjacent organs which erode into stomach or upper intestine; lesions of the small intestine; certain nutritional deficiencies; shock; rupture of aneurysm into the upper alimentary tract; swallowed blood from epistaxis, hemoptysis, or the mouth; vicarious menstruation; and malingering.

History and Examination of Patient with Hematemesis or Melena

Past History. Most ulcers, before they bleed, cause distress for a long period. The average duration of symptoms before hemorrhage occurs in both gastric and duodenal ulcer is approximately 4.5 years.

Predisposing Factors. The relationship of miscellaneous fac
claimed to favor or predispose to hemorrhage from peptic ulcer have
discussed in Chapter 16. Activity has been assumed to predispos
hemorrhage (230), but Blackford and Cole (231) have reported that
thirds of 57 cases of massive hemorrhage occurred during a relat
quiescent period. Only presumptive evidence indicates that excessive
of alcohol, caffeine, and tobacco and dietary indiscretions may predis
to bleeding. Hypertension and arteriosclerosis are more apt to predis
to continued or recurrent bleeding than to the actual onset. A distu
emotional state such as sustained anxiety appears to be a predispo
cause. For example, it has been shown that an increase occurred i
admissions for hemorrhage from peptic ulcer in London during the pe
of the heavy air raids (232).

A Vitamin C deficiency sometimes coexists with a bleeding p
ulcer. Portnoy and Wilkinson (233) found a Vitamin C deficiency in
patients with peptic ulcer with and without hematemesis. The sev
degrees of deficiency were found in patients with hematemesis. Moss
(234) found that peptic ulcer patients, being on a restricted diet,
lower average plasma C levels than the population at large, but
little difference in bleeding and nonbleeding peptic ulcers. Twenty
cent bled with a normal Vitamin C level and the low level persist
those who stopped bleeding. It would appear that a low Vitamin C
does not markedly predispose to hematemesis and melena.

Prothrombin and clotting and bleeding times are usually w
normal limits in patients with bleeding peptic ulcer (234).

Immediate History. The symptoms experienced by the patien
depend on the rate and amount of blood lost and the tolerance of
ticular patient to hemorrhage. In a small hemorrhage, melena or
temesis may be the only symptoms, complete compensation occurr
the vascular system. Sometimes a series of small hemorrhages m
followed by a large one; in such a case, the massive hemorrhage is
to produce more severe symptoms.

After a large hemorrhage, hematemesis or melena and collapse
but not necessarily in that order. The general manifestations of h
rhage, pallor, weakness, faintness, nausea, and sweating may precc
actual appearance of blood in the form of hematemesis or melena w
without tenesmus. These symptoms occasionally present a probl
diagnosis until the blood appears.

Syncope on assuming an erect position, as the result of postural
tension, may occur after the loss of blood. The patient may have a
urge to stool, as the result of hemorrhage, and "black out" on aris

ttempt to arise from bed or a chair on experiencing a sudden nausea, emesis or weakness, and faint on standing.

he history of previous pain or dyspepsia disappearing after hema- is or melena is highly suggestive of peptic ulcer as the cause of ng. This phenomenon does not uniformly occur, however (236).

NIFICANCE OF MELENA AND HEMATEMESIS. Hematemesis alone occurs frequently in gastric ulcer than duodenal, and melena alone more ntly in duodenal or anastomotic ulcer than in gastric. However, a alone may occur with gastric ulcer or hematemesis alone with nal ulcer (p. 560) (Table 53). An example is the report of Baker of five fatal cases of melena without hematemesis, four of which were d gastric ulcers. Melena without hematemesis can occur with geal varices (235) or in hemorrhages from gastritis (238).

is usual for the stools to be black and shiny shortly after a gastro- nal hemorrhage, as the result of the production of acid hematin from lobin by the action of acid or the production of the sulfide of heme he action of H_2S on the iron in the heme. Occasionally, a bloody ay be passed, but such blood is usually in the form of a "currant stool. Nevertheless, in the absence of hematemesis, there may be difficulty in differentiating upper from lower bowel bleeding. In l, blood from the lower intestine and colon is red and is not thor- mixed with the stool, whereas bleeding from the upper alimentary usually rather homogeneously mixed with the "tarry" stool.

ematemesis may contain either bright blood or "coffee ground" al, but neither is diagnostic of any particular lesion. For instance, (239) observed that seven of eight patients with gastric carcinoma d bright blood and 30 of 166 patients with peptic ulcer vomited ground material.

FERENTIATION OF HEMATEMESIS AND HEMOPTYSIS. This is not diffi- ematemesis is frequently mixed with food or gastric juice whereas tysis is bright red and frothy. There is usually a history of cough sputum both before and after may be blood-streaked. Examination sputum and an x-ray film of the chest should effectively rule out g from the lungs. The differentiation is somewhat more difficult lood from the nasopharynx or from the lungs is swallowed and then d. In cases where such is suspected, the presence of cough and treaked sputum and the x-ray of the chest should be of considerable amination of the nasopharynx or posterior nares for clots and old ay clarify the presence or absence of nasopharyngeal bleeding.

SICAL EXAMINATION. Examination of the patient usually gives little ation so far as the etiologic diagnosis is concerned. Jaundice, spider

angiomata, a palpable, firm liver, hemorrhoidal varices, ascites and loss or lack of axillary and pubic hair are physical findings in cirrhosis. An enlarged spleen may indicate chronic passive congestion from hepatic cirrhosis or it may indicate a hemorrhagic disease. An abdominal mass, supraclavicular lymph nodes, or a rectal shelf suggest carcinoma.

Arteriosclerosis is a contributory factor in fatal hemorrhage. While the peripheral and retinal vessels should be examined, sclerosis of large gastric arteries is not proportional to the incidence and severity of sclerosis in other arteries and when present is usually relatively mild in character (240).

Roentgenologic Examination. The x-ray examination of the patient with hematemesis or melena is usually delayed for two to four weeks after the hemorrhage to avoid renewed bleeding. However, when surgical intervention is contemplated, a certain diagnosis is usually desired immediately and during the period of delay some ulcers will have healed and will no visualize when the roentgen examination is undertaken.

Hampton (241), Schatzki (242), and others use a method whereby the examination is made with the patient lying horizontal on the x-ray table and no manipulation is performed. A thin mixture of barium is used and the stomach examined by double contrast, utilizing the air normally present in the stomach. Esophageal varices may also be visualized with this technique. Schiff (239) has used this method in 51 patients with severe hematemesis and melena with no apparent harm. Thirty-one patients were found to have peptic ulcer (Table 123). A crater was found by the

Table 123

Hampton Technique of Roentgen Examination in 31 Cases of Bleeding Peptic Ulcer*

Final Diagnosis	*No. Patients*	*Positive†*	*Suggestion*	*Negative*
Duod. Ulcer.....	25	17	5	3
Gastric Ulcer.....	5	2	..	3
Anast. Ulcer.....	1	..	1	..

* Schiff (239).

† In 4 patients with positive results, subsequent roentgen examination was negative.

Hampton technique in four patients who later did not have a crater roentgen examination, presumably because of healing. Bohmanson (2- has made a practice of early roentgenography since 1930, without observing a complication. It is sometimes advised to have blood ready

nsfusion and surgical facilities available when the Hampton technique employed early (244, 245). On the contrary, some have not found ntgenography performed during or soon after a hemorrhage to be of nificant diagnostic value in so-called "negative" cases (228). Others have pressed the belief that such an examination would start a fresh hemorage. For example, some surgeons have observed, at operation, the ginning of a fresh hemorrhage from an ulcer after a gentle touch which ushed away a clot. Heuer (229) has reported the case of three patients in om a swallow or two of barium apparently started a fatal hemorrhage. It is obvious that the use of roentgenologic examination during and mediately after active bleeding should be undertaken cautiously. How-r, it is not clear why a dilute barium mixture should be more likely to rt a fresh hemorrhage or increase an existing hemorrhage than the early quent feeding of a soft diet.

Gastroscopic Examination. Gastroscoping a patient may also "stir " further bleeding. Schindler (246) has stated, "During the immediate ases of profuse hemorrhage, gastroscopy is contraindicated, but it may undertaken safely as soon as the active bleeding has ceased and the tient is in good condition. . . . If the surgeon insists upon immediate eration, it should be preceded by gastroscopy to determine the source hemorrhage." Schiff (239), Snell (230), and others have employed troscopy in selected patients, apparently under the same circumstances Schindler. Jones (247, 314) has gastroscoped selected cases in three to days after hemorrhage without observing serious complications. He formed gastroscopy in 116 out of 217 cases which clinical and radiologic estigation failed to diagnose. In 86 there were pathologic changes and s group included 65 cases in which there was a gastric ulcer. Thus, two rds of the cases undiagnosed by other methods were diagnosed gastro-pically. Sullens, Steigmann, and Meyer (248) gastroscoped 30 cases of eding peptic ulcer. Four cases of gastric ulcer not seen by roentgen-raphy were seen with the gastroscope, while two seen with the x-ray re not seen with the gastroscope.

Early gastroscopy would seem to be indicated in selected cases where importance of a diagnosis is great, just as is early roentgenoscopy.

Blindness Following Hematemesis and Melena. Amaurosis follow-distant hemorrhage has been known for many years to occur rarely 9). It most commonly follows hematemesis and melena (250) and is said occur more commonly after repeated small hemorrhages than after a gle large one (251). The underlying pathologic change is optic atrophy, the cause is poorly understood. The loss of vision may occur imme-tely or its onset may be delayed for more than 18 days after hemorrhage.

Determination of Gravity of the Hemorrhage

The symptoms of a bleeding peptic ulcer are chiefly those of he rhage, regardless of its source. The rate and volume of the hemorrhage repeated or continuous character of the hemorrhage, and the vari in the response to or susceptibility of different persons to blood los the factors which render it difficult to determine quantitatively the gr of a hemorrhage.

Chronic Blood Loss. Repeated small hemorrhages may produ condition which is referred to as a state of chronic blood loss. In instances, the loss may be so small as to produce no change in the he globin concentration of the blood. Should an anemia result, it doe present the threat to life of acute blood loss, and the symptoms are of hypoxemia. In chronic blood loss, the patient's tissues may be acclimated to a hypoxia, and he may have a rather marked anemia 7.5 Gm. per 100 cc.) without marked symptoms at rest or on mild exe But in general, the patient with an anemia from chronic blood l easily fatigued and complains of lassitude, shortness of breath, fain and palpitation. He is pale and hemic cardiac murmurs are not un mon. A varying degree of hemoglobin depletion (12.0 to 7.5 Gm 100 cc.) may be present and the examination of the blood shows chromic microcytic erythrocytes.

Symptoms of Acute Blood Loss. In acute hemorrhage, there sudden decrease of the circulating blood volume. The clinical p subsequent to this results from a hypoxemia due to a decrease i oxygen carrying capacity of the blood (anemic hypoxia) and chan the blood volume, the size of the vascular tree, and the cardiac outp

Some idea of the relative frequency of gastrointestinal hemorrh different rapidity and severity may be gathered from the observati Allen and Benedict (252). They studied 628 patients with duodena who gave a recent history of manifest bleeding or actually bled in m amounts while under observation. Of these, 40 per cent had no sec anemia, 29 per cent had bled sufficiently to reduce their hemoglo less than 70 per cent and the red blood count to less than 3.0 mill cubic centimeter, and 30 per cent had a marked secondary a However, only 138, or 22 per cent, had a hemorrhage of sufficient s ness and volume to produce prostration, shock, and a marked anemia. Since cases of acute blood loss may lead to death, it is ne that an attempt be made to establish the factors which tend to inc fatal outcome.

Amount and Rate of Blood Loss. An accurate idea of the amount o lost can only rarely be determined from the history. Hematemesis

with gastric contents, and the volume as estimated by patients and es is usually exaggerated. There is now available no accurate d of determining the amount of blood lost in the stools.

e variation in the response of different individuals is demonstrated e observations of several groups of investigators who have rapidly rawn various amounts of blood from their human subjects. In one of experiments (253), 465 to 1150 cc. of blood were withdrawn by ction as rapidly as possible from 27 adult subjects. Sixteen mani- syncope; some who had lost only 465 cc. developed syncope and who had lost over 1000 cc. had no symptoms. In another group of ments (254), 760 to 1220 cc. of blood were withdrawn in from three minutes from six adult subjects; this amounted to from 15.5 to er cent of the blood volume of the subjects. Five of the six collapsed, coming unconscious; the sixth subject had no symptoms. Thus, some may faint on losing 500 cc. of blood and others will have no symp- on losing 1000 cc. within five to 15 minutes.

vertheless, the *occurrence of fainting and diarrhea* appear to be of some ostic significance.

460 patients reported by Sullens, Steigmann, and Meyer (248), the l mortality from hematemesis and melena was 12.2 per cent. Among ients who fainted, the mortality was 21.3 per cent. And among 32 ts who had enough bleeding to produce a diarrhea, the mortality 3.7 per cent.

Table 124

SHOWING VARIATION IN LETHALITY OF HEMORRHAGE IN DOGS*

No. Dogs	*Blood Loss Per Cent*	*Lived*	*Died*	*Mortality Per Cent*
7	45–49	1	6	86
8	50–54	2	6	75
14	55–59	2	12	86
14	60–64	2	12	86
7	65	1	6	86

* Ivy et al. (255).

e amount of blood loss necessary to produce death in acute hemorrhage is to variation, as shown by studies in our laboratory (255). Anesthetized ere bled from one carotid artery during a period of 10 to 15 minutes, il the onset of acute air hunger, or until respiration had ceased; after e carotid was tied. At this time, the flow of blood had stopped or was g in infrequent drops. The mortality rate as compared to the per cent

loss of blood volume is shown in Table 124. It will be seen that animals died after losing 45 to 50 per cent of their blood while others after losing 65 per cent of their blood.

Significance of Site of Ulcer. Whereas the mortality from all b ing peptic ulcers is approximately 8 or 9 per cent, that from ble gastric, duodenal, and anastomotic ulcer is approximately 17, 9. 6 per cent respectively (Tables 69 and 83). Hence, some effort shou made to determine the site of the ulcer. While the course of the ble will determine the ultimate management, a patient with a known g ulcer should be viewed with somewhat greater suspicion.

Significance of Age and Arteriosclerosis. The age of the p with a bleeding peptic ulcer is an important prognostic factor. Eigh cent of deaths occur above the age of 40, and 70 per cent above the 50. Even more striking is the fact that the relative average morta bleeding ulcer in patients below 40 years is approximately 4 pe and above 40 years is 12 per cent, or below 50 years, 5 per cent, and 50 years, 15 per cent. Goldman (256) found that 70 per cent of 38 p dying from hemorrhage had arteriosclerosis.

Age and arteriosclerosis are correlated because the elder patien tinues to bleed due to the failure of the opened vessel to constric retract like the more elastic vessel of youth. The failure of the ve constrict and retract may be due to (a) rigidity of the vessel secc to loss of elasticity or to arteriosclerosis, (b) fixation of the blood by the connective tissue of the scar of a chronic ulcer, and (c) rup only one side of the vessel. This factor of retraction of the vessel i important primarily than the formation of a clot or a fall in blood pr since constriction and retraction of the vessel favor the formation of (257, 258).

Significance of Duration of Symptoms. The duration of symp not a strikingly important factor, since 28 per cent of fatal cases of bl peptic ulcer are acute ulcers (Table 81). But Jones (314) had or deaths in 67 patients with acute gastric ulcer and feels that "acute" as a whole carry a lower mortality. He found that even relapse of bl after admission to the hospital was less dangerous for "acute" lesio for chronic lesions. In referring to "acute" lesions, Jones include gastritis, acute gastric ulcer, and other "x-ray negative" cases.

A patient suffering from a first hemorrhage is in no greater than one who has had a nonrecent hemorrhage (Table 61), all other being equal.

Significance of Persistence and Rapidly Successive Rela Hemorrhage. Most fatalities from bleeding peptic ulcer occur

* The term "recurrence" may lead to confusion. We believe that a he

Table 125

ORTALITY IN RELATION TO RAPID RELAPSES OR PERSISTENCE OF HEMORRHAGE

	Single Arrested Hemorrhage			*Recurrent or Persistent Hemorrhage*		
	Number Cases	*Number Died*	*Per Cent Died*	*Number Cases*	*Number Died*	*Per Cent Died*
nan & Price (260)	70	3	4.3	37	16	41
er & Hartfall (236)	59	5	8.5	80	26	32.5
y & Hurst (295)	67	0	0	15	4	27
es & Nevin (261)	285	28	9.8	106	56	53
(259)	48	0	0	21	7	33.3
r (237)	312	19	6	185	48	26
rsen (297)	242	2	1	61	14	23
ns et al. (248)	190*	14	7.4	14†	8	57.1
s (314)	427	16	3.7	103	26	25.2
otals	1700	87	5.1	585	189	32.3

Bleeding stopped in 48 hours with medical treatment.
Continued or recurred after 48 hours of medical treatment.

Table 126

MORTALITY IN SINGLE AND MULTIPLE RELAPSES OF HEMORRHAGE

Author	*Single Hemorrhage*			*One Further Hemorrhage*			*More than One Further Hemorrhage*		
	Number Cases	*Number Died*	*Per Cent Died*	*Number Cases*	*Number Died*	*Per Cent Died*	*Number Cases*	*Number Died*	*Per Cent Died*
r (237)	312	19	6.0	151	44	29.0	34	14	40.0
nan & Price (260)	70	3	4.3	16	4	25.0	21	12	57.0
otal	382	22	10.3	167	48	29.0	55	26	47.0

hemorrhage persists or because it relapses, particularly after the ent enters a hospital. Where bleeding is arrested, the mortality is 5 per , whereas it is 32 per cent in bleeding which continues or rapidly rs (Table 125). The mortality from a hemorrhage which relapses e than once is almost twice that of a single relapse (Table 126). The

ring after an interval of months or years affects mortality very little (Chapter 16). present use of the term "relapse" applies to repetition of the bleeding during an episode of hematemesis or melena.

data in the literature are too heterogeneous to determine with any de of certainty the relation of mortality to the length of the period betw the initial hemorrhage and a relapse (236, 259, 261, 269). The only c clusion that can be drawn is that an increased mortality can be expe in patients who manifest persistent or successive relapses of hemorrh within a period of 72 hours. This agrees with our clinical experience is supported by various surgeons (259, 262, 263), who advocate in vention within the first two or three days. *The gravity of hematemesis melena is dominated by this notion of "further bleeding."* In the great majo of instances where severe bleeding has continued or rapidly succes relapses have occurred, at autopsy or operation an open vessel is fo at the base of the ulcer.

Clinical Criteria of Grave Hemorrhage

The concept of "further bleeding" or, as some say, "open v bleeding" is the most critical factor in determining the gravity of a he rhage. It is difficult, however, to determine whether further blee represents persistent or successive relapsing hemorrhage (264), but have similar physiologic significance. In general, the diagnosis of "c vessel bleeding" can be made by *repeated* performance of several cli and laboratory tests. Single determinations or single tests are of lin value, particularly in the early stages of hematemesis and melena.

Pulse and Blood Pressure. One of the earliest effects of ga duodenal bleeding may be a sudden "collapse" consisting of pallor, s sweating, nausea, blurred vision, and even unconsciousness. It has indicated that the amount of blood loss necessary to produce the symp of syncope is variable, but that the response may be of some progn significance (p. 835). However, a single determination of the pulse blood pressure is unreliable except in the occurrence of "shock." reasons for this will be briefly discussed.

Several important studies on the effects of controlled blood loss been made in blood donors (253, 254, 265). It was found that the was slightly increased or unchanged and that the systolic blood pre was only slightly depressed before collapse occurred, at which there was a precipitous drop in blood pressure and a transient slowi the pulse. The systolic blood pressure remained below 100 mm., c temporarily or for a prolonged interval up to 24 hours. Repeated obs tions of the pulse rate showed it to be an unreliable criterion of impe collapse or the amount of blood lost. The same is true for patients hematemesis and melena (239).

The posture of an individual suffering from blood loss exerts a m influence on whether syncope occurs. A patient may be comfortable

, but on standing becomes faint or unconscious as the result of postural potension (253, 254). Shenken and his co-workers (265) were able to ide the effects of hemorrhage into three stages of severity. In the *first stage*, subject is symptom-free at rest and has a pulse rate and blood pressure hin normal limits. However, on arising, an undue acceleration of the se rate and some diminution of blood pressure are found. In the *second e*, there are still no noteworthy abnormalities as long as the subject is umbent and at rest. But the upright position cannot be tolerated and cope soon overwhelms the subject if he arises. In the *third stage*, syncopal acks accompanied by bradycardia occur even though the subject is at and recumbent. In a single arrested hemorrhage severe enough to duce the third stage, the stages are reversed in recovery. Should a more ssive hemorrhage occur, or should further severe bleeding occur, the ient goes into shock with the classical picture of profuse sweating, rapid thready pulse, and progressive hypotension.

Certain bodily mechanisms are called into play to counteract the reased blood volume as a result of hemorrhage. In a slow hemorrhage, y occur gradually and more or less keep pace with the hemorrhage. On other hand, in a sudden, severe hemorrhage, these mechanisms lag ind the hemorrhage. Reflex vasoconstriction (266, 267), mobilization lood from the reservoirs (268), and restoration of blood volume by the ue fluids (253, 254, 269–271) constitute the major bodily defenses inst the loss of blood.

Short of shock, then, the blood pressure and pulse are unreliable for determination of the amount of blood lost and give no indication as to ther the bleeding is continuing or will relapse.

The presence of shock on admission to a hospital certainly indicates t a severe hemorrhage has taken place; its gravity depends on the time patient has been in shock. Two papers will be cited to indicate the ersity of the observations made by two groups of careful observers arding the relation of the condition of the patient on admission to a pital to the mortality. Sullens et al. (248) had only 8.4 per cent deaths 78 patients with a systolic blood pressure greater than 100 when they ched the hospital. In 43 patients with a systolic blood pressure of less n 100, there was a mortality of 37.2 per cent. However, the findings of ger and Hartfall (236) are quite different. Thirty-nine patients with natemesis and melena entered in shock; of these, seven, or 18 per cent, d. Eighty-six were in fair condition; of these, 18, or 21 per cent, died. enty-two were in good condition; of these, six, or 28 per cent, died. Obusly, a normal blood pressure may indicate a small, compensated norrhage, a larger hemorrhage with marked reflex vasoconstriction, or reduction of the blood pressure in a hypertensive patient. Such diver-

sity shows that the response of the patient to therapy is the best criterion of the real condition of the patient. This is basically true of all disease.

Response to Therapy and the Transfusion Test. The return of the blood pressure to normal levels and its maintenance there in the absence of syncope indicate that bleeding has stopped. Conversely, collapse and shock under therapy or the failure to maintain a blood pressure which has been returned to normal indicates that further bleeding has occurred. It is on this basis that the estimation of the blood pressure and the pulse have their greatest usefulness and require frequent and repeated determination.

The response to transfusion is the basis of the best method for determining open vessel bleeding and the gravity of the hemorrhage (243, 262, 272). Hinton (273, 274) gives a transfusion of 1500 to 3000 cc. of blood on admission. If the patient remains in shock, he feels surgical intervention is indicated. Hoerr, Dunphy, and Gray (244) state that the indication for emergency operation is best shown by the response to transfusions. They feel that the principal consideration is not the amount but the rate of bleeding, as evidenced by recurrent syncope or shock after the circulation has once been stabilized by transfusion and despite continued transfusion at an average rate of not more than 500 cc. every eight hours.

Laboratory Examinations

Various laboratory determinations have been used to attempt to evaluate the gravity of a hemorrhage. None have proved to be as reliable as desired for reasons to be cited.

Hemoglobin, Erythrocyte Count, and Hematocrit. The determination of hemoglobin, red cell concentration, or hematocrit is of questionable value because in the first few hours after a hemorrhage normal values may be obtained. For example, 500 cc. of blood may be withdrawn from normal human subjects without causing any change in the erythrocyte count for a number of hours (275). Then, the rate at which fluid passes from the tissues to restore the blood volume and dilute the red cells is subject to considerable variation. In well hydrated animals, fluid moves from the tissue into the blood vessels quite rapidly after a hemorrhage (269, 270). In some human subjects, the restoration of blood volume is quite rapid, namely, three or four hours when 500 to 1000 cc. of blood are lost; in other subjects, two or three days are required (253, 254, 271). The maximal dilution of hemoglobin is reached in an average of 32 hours (range three to 90 hours), and then in part it is due to an excessive restoration of plasma volume. It is obvious that recent successive relapses of the hemorrhage and the degree of hydration of the body would operate to modify further the normal extent of variation.

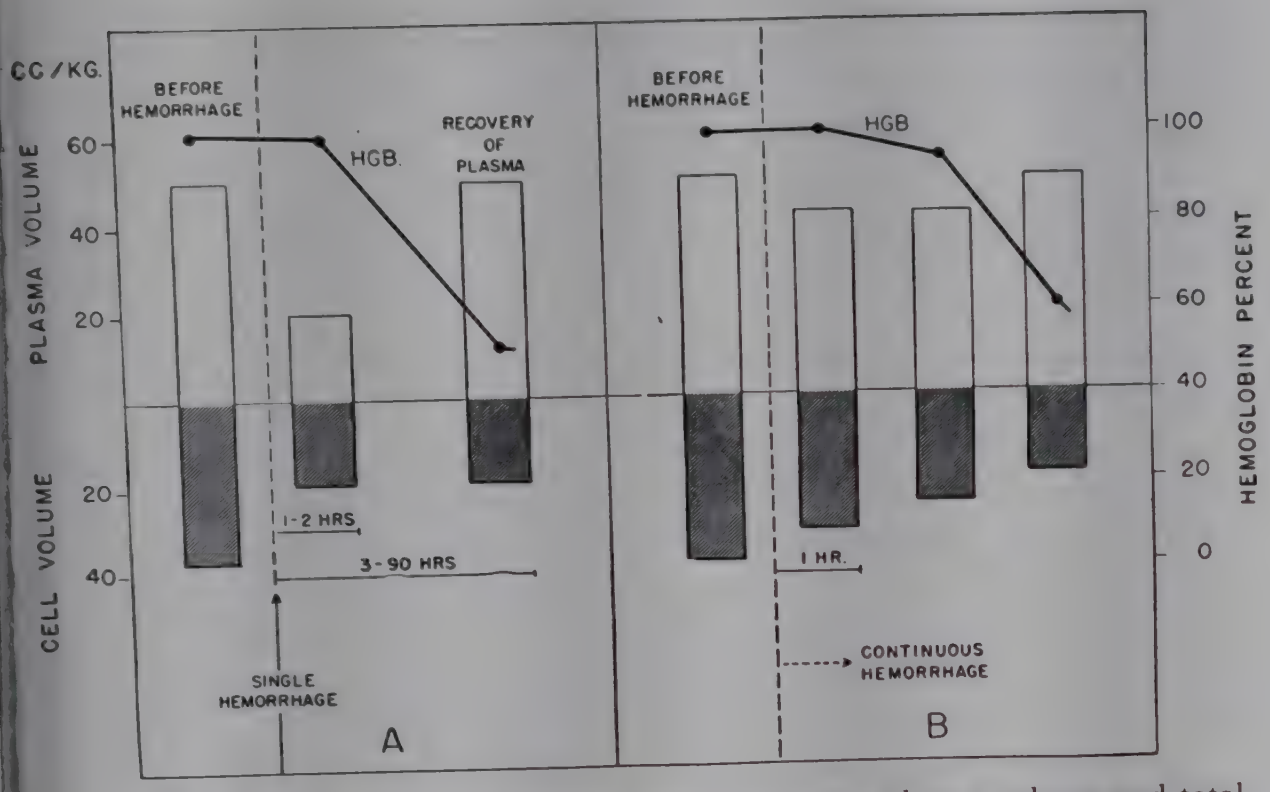


FIG. 130. The relationship between total circulating plasma volume and total circulating red cell volume and their effect upon hemoglobin concentration following a single hemorrhage and with continuous hemorrhage. (Modified from Bennett et al.: *Lancet*, **2**:651, 1938.)

The changes which occur in the relative volume of cells and plasma and the hemoglobin concentration under the simplest conditions of hemorrhage are illustrated in Fig. 130. The diagram illustrates (a) the lag in hemoglobin concentration in the first one or two hours of hemorrhage and (b) that a decreasing hemoglobin and red cell concentration may mean either a continuation of the hemorrhage or a cessation of hemorrhage and a dilution due to the restoration of plasma volume. To this diagram should be added the variations between different patients.

Nevertheless, as is shown by the data in Table 59, the determination of the erythrocyte or hemoglobin level has prognostic value. But it does not have the prognostic value that is desirable, particularly during the first 48 or 72 hours. The determination should be made frequently and routinely, if only to serve as a guide for the need of a blood transfusion.

BLOOD VOLUME DETERMINATION. Because of the uncertainty of the erythrocyte and hemoglobin estimation for the measurement of the extent of blood loss, the use of blood volume determination has been suggested (271) for determining the extent or continuance of bleeding, the need for transfusion, and as an aid in selecting patients in whom surgical treatment may be required. On a theoretic basis the procedure is excellent. The actual volume of blood lost could be accurately estimated

and the presence of further bleeding determined (Fig. 130). U nately, a satisfactory clinical method for accurate determination o volume has not been developed (276).

Red Cell Regeneration. This cannot be used as a measur gravity of a hemorrhage because it does not begin until two or thr after a hemorrhage and is a slow process. It occurs at a constant ra a period approximately 33 days later, when an erythrocyte l approximately 4.5 million per cc. is attained regardless of the levels (277).

Leucocytosis. A leucocytosis occurs in many patients after a rhage from a peptic ulcer, as after a hemorrhage from any othe (280). The extent of increase is variable. The count was found t 10,000 or even 25,000 in 65 per cent of 145 patients (276, 278), w about the same as for cases of hematemesis and melena due to other than ulcer (278). The mechanism of the leucocytosis in hema and melena is presumably the same as that which follows external rhage, since the oral administration of citrated blood does not leucocytosis (278).

Plasma Proteins. After a single hemorrhage, the plasma may be restored in a few hours (253, 254), along with the plasma On the contrary, when plasma protein is removed by plasmap (remove blood, discard the plasma, and reinject the red cells su in normal saline solution), there is no sudden large addition, show under these conditions plasma proteins are steadily regenerated Hemorrhage apparently stimulates the formation of plasma However, the determination of plasma protein is of no value in es the extent of hemorrhage, but is of importance since, if the plasma are low, a transfusion of plasma is indicated as well as of whole b

Fever in Bleeding Peptic Ulcer

Though fever occurs in the majority of patients with hemate melena, irrespective of their cause, it has no bearing on estima gravity of the hemorrhage. In Table 127, a series of 610 bleedi ulcers has been collected. Four hundred eighty-three of these, cent, had a fever. In addition 100, or 81 per cent, of 123 "uncom cases of hematemesis and melena not due to ulcer, had a fever. more apt to occur after a massive hemorrhage (278, 280). The usually appears within 24 hours, lasts from a few days to a week longer, and may reach a maximum of 103° F. The fever is not presence of blood in the alimentary tract, since taking blood o not cause a rise in temperature (278). The exact cause of the fe

Table 127

INCIDENCE OF FEVER IN PATIENTS WITH HEMORRHAGE FROM A PEPTIC ULCER

Author and Ref. No.	No. of Bleeding Ulcers	No. with Fever	Per Cent with Fever
[illegible]*	150	137	91
[illegible]*	24	14	58
[illegible]*	114	83	73
[illegible]ger & Hartfall (236)	133	92	69
[illegible]l & Isenhour (280)	44	35	80
[illegible]iff, Shapiro, & Stevens (278)	145	122	84
Total	610	483	79

* Cited by Dill and Isenhour (280).

Table 128

RELATION BETWEEN AZOTEMIA AND MORTALITY

	More than 100 Mg. Per Cent	70–100 Mg. Per Cent	50–70 Mg. Per Cent	30–50 Mg. Per Cent	Less than 30 Mg. Per Cent
[illegible]. * (284)					
[illegible]es	← 11 →		15	51	55
[illegible]	← 7 →		5	4	0
t Died	← 64 →		33	17	0
[illegible]a. † (242)					
[illegible]ases	2	← 32 →		← 76 →	
[illegible]ied	2	← 4 →		← 2 →	
ent Died	100	← 12.5 →		← 2.6 →	
[illegible]T					
[illegible]ases	3	← 10 →		← 18 →	
[illegible]ied	0	← 5 →		← 6 →	
[illegible]nt Died	0	← 50 →		← 33 →	

[illegible]s represent B.U.N. levels.
[illegible]s represent N.P.N. levels.

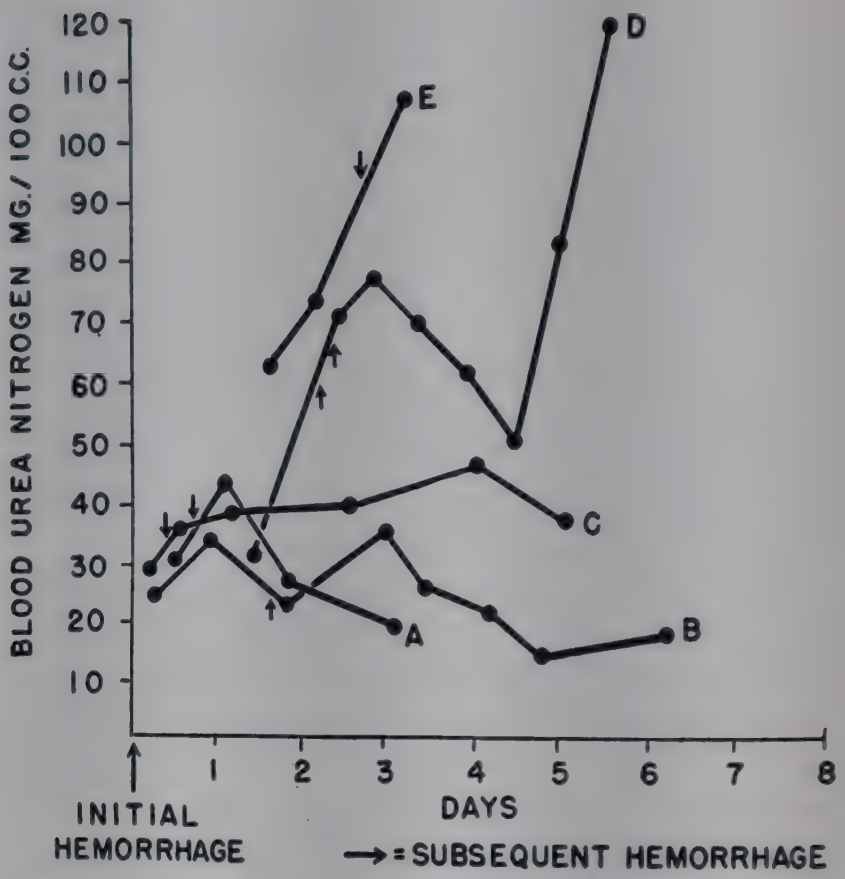


FIG. 131. Blood urea nitrogen levels in some representative cases of bleeding peptic ulcer, showing the effect of relapse of bleeding. Patients A, B, and C stopped bleeding by the second day; D and E did not and they showed a marked secondary increase in blood urea nitrogen. (Modified from Schiff et al.: *Am. J. Digest. Dis.*, **9**:110, 1942.)

certain (276). It may be due to the factor which causes the leucocytosis, though fever occurs more frequently than leucocytosis.

AZOTEMIA WITH GASTRODUODENAL HEMORRHAGE

In recent years, considerable attention has been directed to the occurrence of azotemia with hematemesis and melena. It has been studied relative to its etiology and prognostic value (282). The azotemia is almost entirely due to a rise in blood urea and is accompanied by a normal or an increased chloride concentration and a normal carbon dioxide combining power of the blood (284). Some evidence indicates that blood urea nitrogen levels above 70 mg. per cent portend a fatal outcome (Table 128). But cases of hematemesis ending fatally have occurred in the presence of normal levels (239, 285).

In general, the blood urea nitrogen level follows a rather characteristic pattern in a single nonfatal hemorrhage. It rises rapidly in the first few hours, the maximum concentration being reached in the first 24 to 48 hours, and drops to normal on the third or fourth day. Should a

second nonfatal hemorrhage occur, there is a secondary rise, frequently greater than the first, reaching its peak in the next 24 to 48 hours before dropping back. In fatal recurrent or continued hemorrhage, the blood urea nitrogen continues to rise above the normal or fluctuate above normal without dropping back. These curves are illustrated graphically in Fig. 131. Occasionally a fatal case may demonstrate the single hemorrhage type of curve (284).

Considerable experimental work has been done to ascertain the etiology of the azotemia. Many observers (286–289) have administered large amounts of blood intragastrically and noted a prompt moderate rise in the blood urea nitrogen as the result of the digestion and absorption of a large amount of protein. Blood administered into the colon (286) or lower ileum (290) produces little or no rise.

However, the rise of blood urea nitrogen seen after the intragastric administration of blood does not reach the level seen in some cases of hematemesis or melena, and some investigators (283, 285, 289) believe that the higher levels represent an additional factor of decreased renal function subsequent to decreased blood flow and dehydration as a result of hemorrhage. The presence or absence of decreased renal function associated with azotemia is controversial (283, 289, 291–294).

Hematemesis, Melena, and Examination of Stools

Hematemesis is apt to indicate an acute and possibly severe hemorrhage. Some authors (236, 297) consider death from melena without hematemesis to be so rare that melena alone should not be considered as a threat to life. While fatal cases are heavily weighted towards those having hematemesis (Table 129), it should be recalled that about 70 per cent of patients admitted to hospitals with bleeding peptic ulcer have vomited blood (Chapter 16). It is certain that hematemesis, as a rule,

Table 129

Hematemesis and Melena in Fatal Cases of Bleeding Peptic Ulcer

Author	*Hematemesis*	*Melena Alone*	*Total*
Meulengracht (264)	19	0	19
Babey & Hurst (295)	4	0	4
Hansen (296)	85	12	97
Baker (237)	72 (16 per cent) died in 443 patients with hematemesis	5 (9 per cent) died in 54 patients with melena alone	77

represents more serious bleeding but the occurrence of death patients with melena alone shows that melena is a threat to life

It should be recalled that the entrance of from 50 to 100 cc into the upper gastrointestinal tract will yield a "tarry stool" that a "tarry stool" appears in from four to 20 hours after the in of 1 to 2 L. of blood into the stomach. Mild tarry stools may be from one to four days after one such sustained gastric hemorrh finally, the occult blood may be found for from three to 10 day ingestion of from 75 to 250 cc. of blood and up to 14 days a blood (299, 300).

Use of Indwelling Gastric Tube for Diagnosis of Cont or Early Relapsing Hemorrhage

Soper (301), who has treated hematemesis with an indwell tube, encountered four cases in which bright red blood reappe gastric aspirate. The surgeon found a spurting vessel in each p use of the indwelling tube has not been generally adopted bec of the tube starting a fresh hemorrhage.

Peptic Ulcer in Infants and Children

Peptic ulcer of the newborn (zero to two weeks) usually perforates without premonitory signs. Because of the sudden fulminating symptoms, relatively few of these patients are correct diagnosis and operated upon (302). It is probable that of melena neonatorum are caused by acute ulcers, chiefly of the (303). The occurrence of melena or hematemesis or evidence or an acute surgical abdomen should be considered as possibly complications of a peptic ulcer. In suspected perforation, and flat plate for pneumoperitoneum is indicated, as it may selected cases of melena. Roentgenologic examination is oc cated in cases of suspected stenosis.

After the first two weeks of life and up to one year of ag newborn, most of the ulcers either bleed, or perforate, or do before they are recognized. During this period, cases of sm ulcer occur. Refusal to feed, evidence of abdominal pain, re streaked vomitus, pylorospasm, and loss of weight are symp suggest the presence of ulcer. Certainly roentgenologic should be used in such cases. But in the past, as in the case of relatively few of these patients have been operated upon or recognized prior to autopsy (305).

Between two and 12 years of age, peptic ulcers are more diagnosed with the complication of stenosis than with the

n or hemorrhage. However, according to the literature, the complications of peptic ulcer are as frequently recognizable with peptic ulcer without the complications. This children with abdominal or dyspeptic complaints are not roentgenologic examination as frequently as they should be 17, p. 643).

re is nothing special about the diagnosis of peptic ulcer in children. The important point is to remember that it occurs e roentgenologic examination more frequently in suspected every author who has written on this subject has expressed peptic ulcer in infants and children occurs more frequently enerally realized.

Peptic Ulcer in the Aged

oods of peptic ulcer in elderly persons is not different from adults. However, since 1936 several articles have appeared ve been pointed out that the manifestations of peptic ulcer in the aged. It has been claimed that the symptoms are than in younger patients, especially when the ulcer starts of age, when the acidity of the gastric contents tends to be is the complications of ulcer which more frequently cause ent to seek care (306). A gastric lesion when diagnosed is more likely to be malignant. Perforation is more likely to emorrhage in the mature adult: 73 per cent of perforations 20 and 50 years of age (Chapter 16). The frequency of and hemorrhage increase after the age of 40 (Chapter 16).

be kept in mind that gastric and duodenal ulcer may first e age of 60 (307, 309). Elderly people may develop acute unsuspectedly bleed profusely or perforate (185, 291, 309).

Summary

viewpoint of the patient, the symptoms of peptic ulcer, presence of complications, constitute the disease. The most ristic feature of the disease is the characteristic pattern of Periodicity and periodicity are marks of peptic ulcer. For the history is considered of prime importance in the

Pain, which is present in 90 to 100 per cent of patients with odenal ulcers, occurs commonly in relation to eating, ly appearing within one to three hours after a meal. There distress before breakfast and it may not occur during the ain during the night is common. The pain of peptic ulcer

is variously described as burning, gnawing, crampike, aching, boring, sharp, dull, and severe. Some describe it as a "hung Food and or alkalies usually provide temporary relief.

The pain of small peptic ulcers is usually diffusely localiz epigastrium. But in large and penetrating ulcers, the pain is cisely localized, being in the left epigastrium in gastric ulcer, in t and right epigastrium in duodenal ulcer, and to the left and slig the level of the umbilicus in anastomotic ulcer. When any ulcer into structures posterior to the stomach and duodenum (pa pancreas), the pain tends to become intractable and may be r the back.

Vomiting with or without nausea is a variable occurrence plicated peptic ulcer. Nausea alone is rare. Eructation, "wat heartburn, and constipation may be complaints.

Physical Examination. There are no specific anthro measurements or general appearance which characterize the p patient. In uncomplicated cases, there may be no physica although epigastric tenderness is frequent. Tenderness whic pressure exerted on the ulcer from the outside is referred to a tenderness." "Reflex tenderness and rigidity," due to a visc reflex, occur uniformly when the ulcer penetrates or perfora also be found in many patients in whom the ulcer is not deeply p

Laboratory Aids. While peptic ulcer is virtually unkno presence of true achlorhydria, gastric analysis offers little dia other than detecting the presence or absence of hydrochlor large volume of highly acid juice is suggestive of duodenal ulc more value as a guide to therapy than as a diagnostic point.

The blood count is usually normal in uncomplicated cases vary widely on the occurrence and significance of occult bl stools.

Introduction of 200 cc. or more of 0.5 N hydrochloric ac stomach (the Palmer acid test) will produce pain in 75 per ce of patients with active peptic ulcer. Future investigation may procedure to be of value in those patients who are having di presence of duodenal deformity and the absence of a crater.

Esophageal Ulcer. This is a rare condition. Esophagos visualize all esophageal ulcers suggested by substernal pain o tography.

Gastric Ulcer. A combination of roentgenographic a scopic examination should improve the absolute diagnosis of g Gastroscopy may visualize the 5 to 10 per cent of ulcers not ev

overlooked by roentgenography and roentgenoscopy may
to 30 per cent of ulcers which cannot be seen gastroscopically.
standing problem in the diagnosis of gastric ulcer today is
lation of the benign form from the malignant form of this
rimental, clinical, anatomic, and histologic evidence indicates
elopment of cancer from a benign ulcer of the stomach is a
ent occurrence, and that if a gastric ulcer is found to be
probably was malignant at its inception.
problem narrows itself to the differentiation of benign from
lcers. The seriousness of the problem is indicated by the
ures from a collected series of cases: 17.2 per cent of cases
gastric resection with a preoperative diagnosis of benign
inal diagnosis of carcinoma; 6.5 per cent of medically treated
ally proved to have carcinoma; and 12.7 per cent of all cases
y carcinoma of the stomach masquerading as a benign

roentgenography or gastroscopy is infallible in the differential
benignancy from malignancy, even when used in conjunction.
nis is of aid only when histamine refractory achlorhydria is
peated examinations, indicating malignancy, or a free acid
80 units on a test-meal, indicating probable benignancy.
size of the lesion, the age of the patient, and the duration of
e suggestive but undependable criteria.
of healing is frequently used to differentiate these two types
of the stomach. During a period of rigid medical management
, the symptoms must subside completely, occult blood must
om the stool, and the crater must disappear or show pro-
ling. However, objection has been raised to the therapeutic
rounds that some malignant ulcers will fulfill these criteria.
osis may be made by surgical removal of the ulcer, allowing
st to determine the nature of the disease. The major objection
olicy is that subtotal gastrectomy carries an appreciable

wing items argue in favor of a gastric ulcer being benign:
high acid, lesion on the lesser curvature less than 2.5 cm. in
oentgenologic and gastroscopic opinion of benignancy, and
mediate response to medical management.
Ulcer. When the classical history of duodenal ulcer can
e diagnosis is one of the most certain it is possible to make in
owever, a remission of symptoms may not mean healing of
d, conversely, a recurrence of symptoms may not mean

reulceration of the duodenal mucosa. The diagnostic goal has, therefore, been to perfect objective methods for the demonstration of the ulcer. Fractional gastric analysis is no more informative than an examination of the basal secretion. The latter measure is diagnostic of the presence of an ulcer in the duodenum only in the case of the upper few per cent of patients who secrete more acid than is ever found in normal individuals.

The ulcer crater or niche is the only direct roentgenologic sign of the ulcer. It can be visualized in 60 to 80 per cent of cases. A deformed duodenal bulb means the patient has either an *ulcer* or the *scar* of a healed ulcer. In the absence of a crater, the state of the ulcer must be judged on clinical evidence.

Anastomotic Ulcer. The development of an anastomotic ulcer after a gastroenterostomy or gastric resection is usually indicated by pain and/or hemorrhage. Although the onset may be delayed for as long as 38 years, 70 per cent of cases will have developed within two years of operation. Manifest hemorrhage occurs in 35 per cent of cases and vomiting in as many as 60 per cent of cases. Stenosis of the stoma may occur in 10 per cent of cases and a gastrojejunocolic fistula in an additional 10 per cent.

The roentgenologic diagnosis of anastomotic ulcer is difficult. Craters are seen less frequently than with gastric and duodenal ulcers. Gastroscopy increases the absolute diagnosis, but jejunal ulcers are frequently not visualized.

Differential Diagnosis. Functional dyspepsia is used to specify symptoms referable to the gastrointestinal tract due to functional gastric and duodenal disturbances that are not secondary to detectable organic or functional disease outside the stomach or duodenum. These cases must be differentiated from peptic ulcer.

There are probably two types of functional dyspepsia, "dietary or habit dyspepsia" and "psychoneurotic dyspepsia" with or without an associated gastritis. "Habit dyspepsia" refers to gastrointestinal symptoms referable to the patient's unhygienic habits of living as well as eating.

Even when organic disease of the stomach, duodenum, and esophagus, or reflexly initiated disturbances of the stomach and duodenum, or dyspepsia due to systemic disease are ruled out, a group of patients with epigastric distress or symptoms is left. A cause for the symptoms is not found in 5 per cent of cases and gastritis may account for an additional 14 per cent. The remainder have "psychoneurotic" dyspepsia with or without gastritis. It is possible that emotional states cause the gastritis observed.

Clinically, the patient with psychoneurotic dyspepsia is characterized by the vagueness and multiplicity of complaints and symptoms, psychoneurotic traits or definite psychoneurosis, and relatively little or no relief from ulcer management.

COMPLICATIONS OF PEPTIC ULCER. *Pyloric Obstruction.* Pyloric obstruction associated with peptic ulcer may be functional (reflex) or organic (inflammation or scar tissue). These patients may complain of epigastric distress associated with gastric retention. If high-grade obstruction has been present for some time, the patient will also complain of weakness and loss of weight. If the early morning gastric residium is found to contain food eaten the previous day, it is strongly presumptive that high-grade obstruction is present. Roentgenologic examination is the most accurate way to determine the degree of retention.

Gastric retention occurs in 25 to 30 per cent of patients with peptic ulcer. The obstruction is functional in 80 per cent of the patients with gastric ulcer and about 90 per cent of those with duodenal ulcer, and may be expected to disappear completely or to a large extent on effective therapeutic management.

Hourglass Stomach. In some cases of hourglass stomach, the effect is due to a persistent circular spasm, rather than a scar, and will disappear under medical therapy for the peptic ulcer. The distress of hourglass stomach is mild when present. Vomiting may occur or be induced by the patient.

Perforated Peptic Ulcer. There are two general types of perforated peptic ulcer. The first is "major acute perforation of the acute surgical type"; the second is "minor acute perforation with early spontaneous closure." In major acute perforation, a previous history is absent in 15 per cent of cases. The preoperative diagnosis is made correctly in 83 to 95 per cent of cases. Three stages of the disease are recognized.

The first stage or dramatic stage is usually characterized by abdominal pain, generally sudden in onset. Prostration is common, and nausea and vomiting a variable occurrence. The most common physical finding is abdominal rigidity and tenderness. There may be obliteration of liver dullness and bowel sounds may be absent. In the early stages, the temperature and pulse are usually normal, although costal breathing at an increased rate frequently occurs. Most cases will show a moderate leucocytosis. About 70 per cent of patients will show pneumoperitoneum on radiologic examination.

The second stage, or stage of delusion, may begin in two to six hours. Although the symptoms may seem to subside, the abdominal tenderness and rigidity and the costal breathing persist.

The third stage appears 12 hours or more after perforation and is characterized by generalized peritonitis.

Minor acute perforation with early spontaneous closure (formes frustes) is ushered in by symptoms of major acute perforation, but the pain is not so excruciating and prostration not so great. Symptoms and findings abate in two to 10 hours.

HEMORRHAGE. In a patient with hematemesis or melena, it is necessary

to determine the source and cause of the bleeding and to estab
gravity of the bleeding. Peptic ulcers are responsible for about
cent of cases. Most ulcers have caused distress for long periods bef
bleed, although hemorrhage occurs as the first symptom in about
cent of bleeding peptic ulcers. While in small hemorrhages melen
hematemesis may be the only symptoms, in a larger hemorrhage c
occurs. Examination of the patient usually gives little information
as the diagnosis of peptic ulcer is concerned, although occasionally
causes of hematemesis and melena may be evident by physical ex
tion. Roentgenologic and gastroscopic examination during and i
ately after active bleeding must be undertaken cautiously but are
in selected cases.

The symptoms of bleeding peptic ulcer are largely those of hem
regardless of its source. The mortality is higher in the presence of a
of fainting and diarrhea and of a blood pressure below 100 mm. Hg
hemoglobin concentration of less than 7.5 Gm. per 100 cc. at the
hospital admission, particularly when the patient is over 45 or 5
of age. Bleeding from a gastric ulcer is more hazardous than from
denal ulcer, which is in turn more hazardous than bleeding f
anastomotic ulcer. While hematemesis represents a more acute
bleeding, deaths from melena alone do occasionally occur.

Most fatalities from bleeding peptic ulcer occur because the
rhage persists or an early relapse occurs, particularly after enteri
pital. In patients in whom bleeding is arrested, the mortality is 5 p
whereas if it continues, it is 32 per cent. The mortality increa
multiple relapses. The gravity of hematemesis and melena is do
by the concept of persistent or early relapsing hemorrhage.

The actual estimation of the amount of blood lost is difficult.
difficult to determine if further bleeding represents continuance o
of the hemorrhage because of the variable lag in the restoration o
volume. Blood volume determinations may indicate the actual a
blood lost and the presence of further bleeding, but its usefulness i
by availability and technical factors. Mortality is increased with hi
of blood urea nitrogen and a rising azotemia or failure of the bl
nitrogen to drop towards normal portends a fatal outcome. Pr
of melena or occult blood in the stools for three or four days
necessarily indicate that bleeding is continuing.

Single determinations of the pulse and blood pressure are p
guides to the gravity of a gastrointestinal hemorrhage. But the
determination of the pulse and blood pressure, while the patient
therapy, constitutes a most reliable, although not certain, gu
gravity of the hemorrhage and to further bleeding. If, after ade

patient remains in shock or has recurrent syncope, or the hemoglobin not significantly increased, the situation is grave and surgical intervention should be strongly considered.

Ulcer in Infancy and Old Age. Peptic ulcer occurs in infants and children and in the aged. In the first year of life, most of the ulcers either perforate and may not be diagnosed prior to autopsy. Although ulcer may produce symptoms in older children, the disease is usually not recognized until a complication has occurred. Elderly patients may not seek care until a complication occurs, since the symptoms of ulcer in the aged tend to be mild.

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PART IV

The Treatment of Peptic Ulcer

Introduction

The history of the treatment of peptic ulcer reveals that many fallacious leas have arisen, primarily because it is a disease characterized by remissons and exacerbations during its usually protracted course. Hence, to eep the thinking clear, it should be constantly remembered that the eatment of this disease must be directed *first* to the discovery of the best ıethod for the care of the acute exacerbation and complications of the sease and *second* to the discovery of the best way to prevent recurrences the disease.

Therapeutic Nihilism

Inasmuch as early, uncomplicated peptic ulcer may heal spontaeously, some have advocated a policy of no or minimal treatment, ırticularly early in the course of the disease. *Theoretically*, the medical eatment of ulcer should be pursued energetically in the earliest uncomicated cases for several reasons. It would appear that the completeness ith which an original ulcer heals is a factor in the prevention of recurnces of the ulcer. An ulcer almost, but not completely, healed should be ore subject to the aggressive forces favoring a recurrence than a cometely healed ulcer. We (1) have demonstrated experimentally that a mpletely healed ulcer scar appears to be even more resistant to ulcerain than the surrounding normal mucosa. Also, other factors being equal, e duration of the open lesion must be an important factor in the amount scarring and deformity which results. Furthermore, failure to institute ıreful treatment early in the course of the disease is the loss of an opporınity which should be exploited in the treatment of all chronic recurrent seases, namely, the early application of therapeutic and preventive easures.

Fallacy of *Post Hoc, Ergo Propter Hoc* Reasoning

In all branches of medicine, it is necessary to exercise caution in cribing the improvement which may occur under a given therapeutic gime to the therapy itself. The best control possible should always be nployed; else, spontaneous remissions will be construed to be the result therapy. This error is particularly prone to occur in the assessment

of the efficacy of remedies for peptic ulcer because of the tendency toward spontaneous remission, and also because of the beneficial effect of the reassurance and psychotherapy which inevitably accompanies the administration of any medical procedure, particularly a new method of treatment (2).

Design of an Investigative Therapeutic Study of Peptic Ulcer

There are three ways to design a controlled study of the effectiveness of two or more treatments in a disease like peptic ulcer. In one design, one group of patients receives a certain treatment and a second group another treatment. A second approach consists in using the past record of the patient as the control. The third method consists of a combination of both designs, or the method of paired controls.

Acute Exacerbations

When comparing two forms of medical therapy designed to take care of acute exacerbation, it is obviously best to use the "paired method," in which patients with equal degrees of severity of the disease are alternately or equally divided between the two groups. Our experience teaches that it is very difficult to pair patients with peptic ulcer according to the severity of the disease. Hence, patients as they are seen may be alternated between the groups. In this case, if the groups are sufficiently large, for example, 50 or 100 in each, the error due to random sampling will not be very large. Whether the "paired method" or the "alternating method" of forming the groups is used, the equality of the groups should be compared as regards the duration of the disease, the frequency of the recurrences, the presence or absence of a detectable crater and evidence of penetration, the size of the crater, the degree of retention, the presence of melena and hematemesis, the severity of the pain, and the age and sex. Having as homogeneous groups as practically possible, then the rate of disappearance of symptoms, including occult blood, the rate of healing of the crater, and the disappearance of retention should be followed at regular intervals, preferably weekly. The difference in the averages between the two groups should be checked for significance by statistical methods. This method for comparing the effectiveness of two or more therapies for the care of the acute exacerbations of peptic ulcer has rarely been used.

The method most commonly used has been to obtain a clinical impression of the effectiveness of a new medical therapy. This is done by applying the new therapy to all patients as they are seen and to report the clinical results as "complete relief," "improved," and "failures." This is a hazardous method and is one of the reasons why so many different methods for the management of the acute exacerbation of peptic ulcer exist; the

er reason is that the basic principles are the same in all of the most cessful medical managements. This method is obviously subject to the or in logic of "*post hoc, ergo propter hoc*" reasoning.

In using the patient as his own control, the patient is on a therapy for exacerbation and has not been completely relieved. Then, the therapy nodified or something added to it. In this instance, it is necessary to ume that the patient would not have improved on the original therapy had been continued a few days or a couple of weeks longer. According chance, the results might have occurred if the initial treatment had been tinued, the patient might not have changed or he might have become ter or worse. Unless a good past history with the results of roentgenoic examination is available, this method is hazardous. (A record should made, of course, of the rate of disappearance of symptoms and the rate healing.) The importance of the reassurance some patients receive n the use of a new therapy must be considered in the interpretation of results and is difficult to control in this as well as the other methods evaluating the effectiveness of therapy for the acute exacerbation of disease.

Prevention of Recurrences

A review of the early history of the treatment of peptic ulcer shows that therapy was medical and that it was designed to care only for the acute cerbation. It was not until after the advent of aseptic surgery, the oduction of the operation of gastroenterostomy (1893) for peptic ulcer its widespread use for the treatment of duodenal ulcer in the early of this century, and then the occurrence of postoperative anastomotic r that keen interest in the prevention of recurrences of ulcer was used. After the surgeon entered the therapeutic field of peptic ulcer, the rnist and surgeon started to compare the mortality, morbidity, and rrence rate of their respective therapies and steps were taken to rove the results of medical and surgical therapy. Today, the prevention ecurrences and a reduction in the morbidity and mortality of the ase comprise the paramount problem.

In designing an investigation to evaluate a therapy as regards the preion of recurrences, the effects of psychotherapy are not involved to extent that they are in the care of the acute exacerbations; however, it ore difficult to obtain the cooperation of the patient over a period of or more years than it is over a period of a few weeks. Unless a large portion of the patients treated are followed for two or more years, the lts are likely to be overweighted with patients of the type who are more e to follow hygienic living habits.

n most of the articles in the literature which provide results on the

recurrence of ulcer, the patients are used as their own control without giving the recurrence rate of the patient prior to the application of the treatment. For example, a treatment has been applied to a group of patients and the number of recurrences is given for various periods of time, which frequently are different in the different articles. The best way to present such data is to give the number of patients observed with and without a recurrence for one year, for two years, for three years, or for each annual period for as long as the observation extends (see Table 147, which gives our enterogastrone results). Some articles, unfortunately, do not define what the authors call a recurrence, or a satisfactory or unsatisfactory result. A recurrence may mean (a) the recurrence of abdominal complaints, which might be due to something else than a return of the ulcer, or (b) the recurrence of ulcerlike symptoms with or without the detection of a crater or a change in deformity or irritability of the duodenum or stomach. We believe that the return of ulcerlike symptoms which cannot be clearly attributed to a dyskinetic or spastic colon or disturbances in other viscera should be called a recurrence. It is possible to grade the severity of a recurrence provided it is done by two observers and it can be shown that the two observers check well. In this connection, it should be kept in mind that the criteria for surgical intervention vary widely. In some clinics, all ulcer patients are subjected to surgery; in others, only those patients who do not respond well to medical management. Because of the heterogeneous nature of the populations in many of the articles, a wide variation in the results should be expected. A fair cross-section of the results can be obtained only by considering the results of a number of articles.

It is obviously necessary for every ulcer patient to receive some management for the recurrence after consulting a physician. Furthermore, the management must be different if the ulcer is penetrating than if it is causing more or less continuous distress on an ambulatory management with the patient at work. One obviously starts, as in the case of acute exacerbations, with a variation between patients. Thus, the suggestions made for the design of an investigation for the evaluation of a therapy for acute exacerbations apply also to the prevention of recurrences. The ideal method is to combine the two group design with the design of using the patient as his own control, provided a good two year history is available. When facilities are limited, the selection of so-called "intractable patients" with a good history for two or more years is a practical method which may yield statistically significant differences.

If a large group of ambulatory ulcer patients is available and subject to recall for examination over a period of several years, a new medical therapeutic agent could be evaluated in regard to the prevention of

recurrences by placing all the patients on a standard ambulatory management and giving alternate patients the new therapeutic agent.

The medical, radiologic, and surgical treatment of peptic ulcer and its complications will be considered in this part of the book. In doing so, we shall present the evidence available in support of each therapy, realizing that it has limitations due to the difficulty of designing and, especially, conducting ideal therapeutic studies on this disease. It should be kept in mind that the science of medicine has two aspects, the descriptive and the experimental, and that the study of etiology and, especially, therapy is entirely experimental. Success in therapy is usually only partial; a 100 per cent success with any therapeutic procedure is rarely, if ever, obtained.

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CHAPTER 22

Medical and Radiologic Treatment

Introduction

In 1828 Abercrombie (4) recommended milk and farinaceous foods, ime water (an alkaline drink), and bismuth subcarbonate (demulcent) or the treatment of peptic ulcer. Soda, magnesia, and chalk were recom-nended by Johnson (3) in 1831 "for pain in the stomach due to acidity" 5). Cruveilhier (6) in 1835 recognized that dietary hygiene was important n the prevention of recurrences. The importance of rest was emphasized by Fox in 1872 (198). Thus, the concepts involved in the modern medical nanagement of uncomplicated peptic ulcer, with the exception of the use f sedatives, antispasmodics, "continuous neutralization," and psychiatric onsiderations, were introduced prior to 1880.

Theoretically, the therapy should be directed toward decreasing the ggressive factors and increasing the defensive factors. The aggressive actors are mechanical and chemical. The mechanical consist of rough ood and tonic or spastic gastric motility and retention; the chemical onsist of acid gastric juice and chemical and caloric irritants in the food nd drink. The defensive factors consist of the resistance of the mucosa to nechanical and chemical injury and the healing potential in which ascular, nutritional, and hormonal conditions or mechanisms are nvolved.

Reduction of Acidity of Gastric Contents

This is considered the basic principle of the therapy of peptic ulcer for wo reasons. First, acid plays an important, if not essential, role in the ause of pain (p. 724). Second, acid plays an important role in the etiology nd chronicity of peptic ulcer (p. 765). It is very probable that any treat-nent which would cause a complete abolition of the secretion of acid vithout undesirable side effects would be infallible for the management nd prevention of recurrences. For these reasons, we shall outline the physiologic rationale of the methods for the control of gastric acidity.

Aim of Antacid Therapy

The degree to which gastric acidity should be reduced is an important uestion regarding which there is no general agreement. Reference to the

discussion on pages 75–77 indicates that a pH of less than 4.0 (salmon pink to Töpfer's reagent) in fibroblasts or epithelial cells will destroy them. At this pH, pepsin is only slightly active. What pH in the gastric contents will yield a pH of 4.0 in the fibroblasts or cells of granulation tissue is uncertain, but it probably cannot be much less than pH 2.0 or 3.0. The proteolytic activity of pepsin is almost absent at a pH of 4.5 (Töpfer's reagent reacts yellow), and the digestion of egg white is very slight at a pH of 3.5 (7, 8). In this connection, it should be recalled that a pH of 4.0 represents a dilution of 1/10,000, or 0.00036 per cent HCl, which is a weak acid solution. It may be that a pH of 2.0 (0.036 per cent HCl) or of 3.0 (0.0036 per cent HCl) will not deleteriously affect the pH of proliferative cells which receive a good blood supply (see Table 130 for a comparison of the various equivalent modes of expression of acidity).

Table 130

EQUIVALENTS FOR EXPRESSING ACIDITY

Clinical Units	*Milli-equivalents per Liter*	*Per Cent*	*Milligrams per Cc.*	*Normality*	*pH*
170	170	0.620	6.20	0.17	0.88
160	160	0.583	5.83	0.16	0.90
150	150	0.547	5.47	0.15	0.93
140	140	0.510	5.10	0.14	0.96
130	130	0.474	4.74	0.13	0.99
120	120	0.438	4.38	0.12	1.02
110	110	0.401	4.01	0.11	1.06
100	100	0.365	3.65	0.10	1.10
90	90	0.328	3.28	0.09	1.14
80	80	0.292	2.92	0.08	1.19
70	70	0.255	2.55	0.07	1.24
60	60	0.219	2.19	0.06	1.31
50	50	0.182	1.82	0.05	1.38
40	40	0.146	1.46	0.04	1.47
30	30	0.109	1.09	0.03	1.59
20	20	0.073	0.729	0.02	1.76
10	10	0.036	0.365	0.01	2.04
5	5	0.018	0.182	0.005	2.33
1	1	0.0036	0.036	0.001	3.01
0.1	0.1	0.00036	0.0036	0.0001	4.00

It may be argued that the pH of the gastric contents should not b reduced to a pH of 4.0 or more because at such a level acid no longe stimulates the secretion of pancreatic juice (9, 310) and pancreatic juic helps neutralize acid chyme in the duodenum and promotes intestin

igestion. However, it may be rejoined that if the chyme is less acid than H 4.0, pancreatic juice is not needed to neutralize and that many patients ith anacidity do not suffer an insufficiency in intestinal digestion.

If we assume that "adequate neutralization" ranges from pH 3.5 to 4.5 r even as low as pH 2.0 or 3.0, the question arises regarding the need of naintaining that level continuously throughout the day and night. As ndicated elsewhere, the time of contact as well as the concentration of an cid solution is an important consideration in the acid injury of cells. Sippy (10) felt that continuous neutralization during the day with gastric spiration before retiring was adequate. Winkelstein (11) felt that con-inuous neutralization during the day and night was important, and he ntroduced the continuous intragastric drip. At the other extreme, some se antacid therapy without regard to its effect on the acidity of the gastric contents, and still others use, in most patients, only frequent feedings of a iquid, or mechanically soft, or chemically bland diet (12).

Whether antacid therapy is effective can only be determined by the herapeutic results. However, before this is presented, it is appropriate to consider the methods of administration and the relative acidity-reducing effectiveness of the various antacids.

Methods of Administration of Antacids

Antacids have been primarily employed (1) symptomatically, or (2) between meals and before retiring, or (3) between hourly feedings from 7 or 8 A.M. to 7 or 9 P.M., as in the Sippy management, or (4) as a con-inuous intragastric drip in a mixture of milk and cream as described first by Winkelstein (11). The introduction of the latex nasogastric tube in 1937 by Woldman (13) rendered the continuous intragastric drip more olerable.

Antacid Materials: Theoretical Relative Potency and Other Properties

A vast number of antacid substances are available. Since peptic ulcer s such a common and chronic disease, considerable attention to proposed remedies is given in medical and lay publications. The choice requires careful analysis of the available evidence.

Certain Foodstuffs. Certain foodstuffs are considered as antacids for several reasons. The first is to emphasize their acid combining prop-rties; the second is to promote consideration of the nutritional require-nents of the peptic ulcer patient.

Milk and Cream. Many studies have been made on the antacid prop-rties of milk, cream, combinations of these, and alkalinized milk and milk products.

Titration experiments *in vitro* have shown milk to be moderately efficient as an antacid (8, 14, 15). It has been demonstrated that milk buffers an equal volume of gastric juice to pH 4.0 (16).

The combining or neutralizing powers of whole milk, milk powder, casein, and soya bean "milk" powder are shown in Table 131.

Table 131

THEORETIC NEUTRALIZING OR BUFFERING VALUE OF VARIOUS ANTACIDS ACCORDING TO *in Vitro* CALCULATIONS AND TITRATIONS

Antacid	*Amount of Antacid Used*	*Cc. of 0.5 Per Cent (0.143 N) HCl Neutralized*
Sodium bicarbonate	4.0 Gm.	333 cc.
Calcium carbonate	4.0 Gm.	560 cc.
Tribasic calcium phosphate	4.0 Gm.	361 cc.
Magnesium oxide (MgO)	4.0 Gm.	1380 cc.
Magnesium trisilicate*	4.0 Gm.	768 cc.
Magnesium carbonate	4.0 Gm.	660 cc.
Tribasic magnesium phosphate	4.0 Gm.	427 cc.
Milk powder	4.0 Gm.	25 cc.

* Anhydrous. U.S.P. requires that 1 Gm., calculated on the basis of anhydrous weight, shall combine with 140 to 160 cc. of 0.1 N HCl (0.36 per cent) in four hours.

1 Gm. of casein will combine (pH 3.5) with 5.2 cc. of 0.1 N HCl.

1 Gm. of soya bean "milk" powder will combine (pH 3.5) with 9.5 cc. of 0.1 N HCl.

12.5 cc. of *aluminum hydroxide gel* (4 per cent Al_2O_3) will raise the pH of 150 cc. of 0.1 N HCl (0.36 per cent) from 1.0 to 3.5 in 20 minutes by actual titration (U.S.P.).

30 cc. of *aluminum phosphate gel* (4 per cent $AlPO_4$) will raise the pH of 150 cc. of 0.1 N HCl (0.36 per cent) from 1.0 to 2.4 in 20 minutes by actual titration (U.S.P.).

Milk buffers the "free acid" (3.5 to 4.0) in an equal volume of 0.1 N HCl (0.36 per cent).

100 cc. of 10 per cent *protein hydrolysate* (Amigen) will buffer the "free acid" (pH 3.5) in an equal volume of 0.1 N HCl (0.36 per cent).

Bismuth subcarbonate has only a negligible neutralizing action.

Protein Hydrolysates. These vary in regard to their capacity to neutrali or combine with acid. One gram of some of them will combine at a pH 3.5 with 15 cc. of 0.1 N HCl; 1 gram of others with only 6 cc. The b preparations possess about twice the buffering power of casein or m powder.

MEDICINAL ANTACIDS. The medicinal antacids are frequently divid into two groups; first, those in which acidity is reduced by "reactive sol

on," and, second, by adsorption. In the first group, the speed and egree of solution influence the nature of the reaction. Most of the -called "insoluble" or "nonsystemic" antacids are included in this first roup because they dissolve in dilute hydrochloric acid. The second group onsists of "colloidal" or "nonreactive" materials. They are only "non-active" to the extent that they adsorb hydrochloric acid or act by ion change without chemical reaction. Most of these react chemically, owever, and the classification is of limited value.

The relative *theoretical* neutralizing capacity *in vitro* of several mineral ntacids is shown in Table 131. The method used by Johnson and Duncan 74) is more accurate. Their values are given in Table 132. Their relative eutralizing capacity *in vivo* will be discussed later.

Table 132

THEORETIC NEUTRALIZING OR BUFFERING VALUE OF VARIOUS ANTACIDS*

	Equivalent Dose†•	*Neutralizing Power*‡
Magnesium oxide	0.23	432
Aluminum hydroxide gel	0.40§	280¶
Calcium carbonate	0.57	175
Compound bismuth powder	0.62	162
Sodium bicarbonate	0.85	118
Magnesium phosphate	0.87	115
Aluminum Hydroxide powder A	1.2	130‖
Magnesium trisilicate	1.2	92‖
Calcium phosphate	1.3	74‖
Aluminum hydroxide powder B	3.0	54‖
Aluminum trisilicate	5.0	36‖

* From Johnson and Duncan (174).

† *Equivalent dose:* Weight in grams of substance necessary to effect neutralization of 100 ml. of 0.1 N HCl at 37° C. with stirring in 10 minutes.

‡ *Neutralizing power:* Ml. of 0.1 N HCl neutralized in 10 minutes at 37° C. with stirring by 1 Gm. of substance.

§ Approximately 6.63 Gm. of 6 per cent gel.

¶ Approximately 16.7 Gm. of 6 per cent gel.

‖ Neutralization was not complete at 10 minutes.

Sodium Bicarbonate. This alkali has been and still is widely used. *In vivo* action is rapid. The reaction with HCl is:

$$NaHCO_3 + HCl \rightarrow NaCl + H_2CO_3(H_2O + CO_2).$$

It is to be noted that sodium chloride is readily absorbed and that the Cl^- comes from the blood and returns to the blood in equivalent amounts;

the Na^+ coming from the outside and adding to the base or alkali of body must be excreted, primarily in the urine. Some of the CO_2 eructated; some is absorbed into the blood and expired. All the sod in $NaHCO_3$ contributes toward alkalosis. For this reason, it should ne be given as the sole source of antacid in the management of peptic ulc

Calcium Carbonate. This alkali, which reacts slightly more slowly neutralizes by weight more acid than sodium bicarbonate, is widely us It reacts with HCl as follows:

$$CaCO_3 + 2HCl \rightarrow CaCl_2 + H_2CO_3(H_2O + CO_2).$$

It is to be noted that Cl^- comes from the blood and may return to blood in equivalent amounts. The Ca^{++} comes from outside the body the question is how much of it is absorbed to cause an increase in the of the body. Calcium differs from sodium in that most of it is not sorbed. Most of the calcium chloride formed in the stomach is change relatively insoluble salts in the alkaline or very slightly acid intest contents ($CaCO_3$, $CaPO_4$, and calcium soaps). This explains constipating action of calcium carbonate. The calcium chloride wh absorbed adds base to the body. (Ingested calcium chloride prod acidosis, since the *net* ionic balance which results appears as though s Ca were absorbed along with NaCl + HCl, and the rest of the cal were excreted as carbonate, phosphate, or soap.) Studies on cal absorption, however, show that on the oral administration of 1 Gm. of calcium, rarely more than 0.6 Gm. is retained, and that on incre the dose above 1 Gm. a day, the net retention is not significantly incre During lactation in women, there may be a negative calcium balance an absorption of 3 Gm. of calcium. This is attributed to the limited a to absorb calcium even in the presence of a need, though this has not proven.

Calcium carbonate is frequently mixed with sodium bicarbonate example, the No. 1 Sippy powder consists of 2 Gm. of sodium bicarb and 0.65, 1.3, or 2 Gm. of calcium carbonate. The powder contai Gm. of each will theoretically neutralize 446 cc. of 0.5 per cent HC

A patient receiving large doses of calcium in any form shoul receive large doses of Vitamin D.

Magnesium Oxide (MgO). This alkali acts very promptly and by w neutralizes more acid than either of the previous two antacids ment It reacts with HCl as follows:

$$MgO + 2HCl \rightarrow MgCl_2 + H_2O.$$

aqueous solution, the hydroxide is formed, which reacts as follows:

$$Mg(OH)_2 + 2HCl \rightleftarrows MgCl_2 + 2H_2O.$$

e magnesium ion is poorly absorbed. The available evidence shows om 60 to 85 per cent or more of an orally administered dose may be ered in the feces (17). $MgCl_2$, being quite soluble, exerts an osmotic and prevents water from being absorbed or extracts it from the and hence serves as a laxative. The laxative dose of MgO is 1 to Since relatively little Mg ion is absorbed, the magnesium salts do ntribute significantly toward an alkalosis. Enough is absorbed that should not be given in the presence of nephritis because failure to the absorbed magnesium leads to depression of the central nervous and dilation of the heart.

agnesium oxide (heavy) is frequently combined with sodium nate or calcium carbonate. It counteracts the constipative action cium carbonate. The No. 2 Sippy powder consists of 0.65 Gm. each gnesium oxide (heavy) and sodium bicarbonate and will theoretically alize 278 cc. of 0.5 per cent HCl.

agnesium Carbonate. This alkali, which has been frequently used as an d, acts quite promptly, but by weight does not neutralize as much as the oxide. The laxative dose is 2 to 8 Gm., or twice that of the Since the oxide neutralizes twice as much acid as the carbonate, the of laxative to antacid action is the same for both compounds.

Magnesium Phosphate. This salt of magnesium has also been as an antacid. It reacts theoretically as follows:

$$Mg_3(PO_4)_2 + 6HCl \rightleftarrows 3MgCl_2 + 2H_3PO_4.$$

neutralizes more acid than an equivalent weight of sodium bicare and is laxative. Because of the phosphoric acid produced, a neutral on or pH is not attained.

Calcium Phosphate. This antacid reacts with acid as follows:

$$Ca_3(PO_4)_2 + 6HCl \rightleftarrows 3CaCl_2 + 2H_3PO_4.$$

theoretically neutralizes acid about like an equivalent weight of m bicarbonate and tends to be constipating. Because phosphoric acid duced, a neutral reaction or pH is not attained.

Colloidal" or "Relatively Nonreactive" Compounds.

agnesium Trisilicate. This antacid has been used because it reacts with more slowly than any of the preceding antacids. Some 10 minutes

are required for it to manifest most of its neutralizing potency *in vitro*. It reacts as follows:

$$Mg_2SiO_3 \cdot 2H_2O + 4HCl \rightarrow 2MgCl_2 + SiO + 4H_2O.$$

Magnesium trisilicate does not react completely even in 30 minutes or 1 hour at the pH of gastric juice. This nonreacted portion adsorbs some HCl (18, 19). It is important to use only U.S.P. preparations, since wide variations in properties are found (19–23). It is slightly laxative as compared to equivalent amounts of magnesium oxide or carbonate; because it reacts more slowly, all is not converted to $MgCl_2$. The U.S.P. XIII specifies that 1 Gm., calculated on the basis of anhydrous weight, shall combine with 140 to 160 cc. of 0.1 N HCl in 4 hours. For the tablet form the standard is 85 to 110 cc. of 0.1 N HCl per Gm.

Aluminum Hydroxide Gel. Because only traces of aluminum are absorbed from the intestine and because aluminum gels have the property of reacting slowly with HCl, this compound was introduced and used extensively as an antacid. It reacts with hydrochloric acid theoretically as follows:

$$Al(OH)_3 + 3HCl \rightarrow AlCl_3 + 3H_2O.$$

Aluminum chloride is an acid salt and the final pH never becomes more alkaline than pH 3.5 or 4.0. The standard is that one volume of gel should "neutralize" 12.5 to 25 volumes of 0.1 N HCl.

The $AlCl_3$ which enters the intestine is converted into insoluble $Al(OH)_3$, $AlPO_4$, and $Al_2(CO_3)_3$.

Powdered Aluminum Hydroxide. The U.S.P. XIII requires that 1 Gm. of the powder neutralize 250 cc. of 0.1 N HCl.

Zirconium hydroxide has been studied, but it is not as efficient in neutralizing acid as the aluminum gels (24, 25).

Aluminum Phosphate Gel. Aluminum phosphate was introduced because in the absence of OH^- ion in the intestine resulting from a deficiency of pancreatic juice, phosphate is diverted from the blood plasma in appreciable quantities (2). Aluminum phosphate reacts with HCl as follows:

$$AlPO_4 + 3HCl \rightarrow AlCl_3 + H_3PO_4.$$

When plenty of milk is taken with aluminum hydroxide, the phosphate in the milk can provide phosphate for the aluminum. Otherwise, the urine becomes clear of phosphate and the blood may become depleted (2, 2

Aluminum phosphate in a 4 per cent gel neutralizes only about half as much acid as aluminum hydroxide and it does not raise the pH above 2.5. The U.S.P. XIII specified that one volume of the gel should combine with 5 to 9 volumes of 0.1 N HCl.

Synthetic Resins. These resins raise the pH of gastric juice entirely by sorption (27, 28). Using three times the amount of resin, the titration rve is closely comparable to aluminum hydroxide gel with or without agnesium trisilicate (28). Since adsorption depends on surface, the timal effect is obtained with a fine mesh powder and agitation. They relatively nontoxic but may exert a laxative action due to their bulk 7–29).

Bismuth Salts. The bismuth salts, the subcarbonate and nitrate, have en used for many years in the management of peptic ulcer and irrita- ity of the colon. They have no significant neutralizing value and if they of value, other than in colonic flatulence and irritability, their mode of ion is not clear. It has been suggested that bismuth salts coat the ulcer, t this has not been demonstrated.

Gastric Mucin. Gastric mucin is primarily an emollient, although as epared commercially it possesses some acid-combining power (30, 31). out half of the acid-combining power at pH4 is due to the presence of ptones (32). One gram of some commercial preparations will combine th 15 to 18 cc. of 0.1 N HCl (33); this is small compared to the ant- ds listed above.

Comment. If the reader carefully compares the theoretic order of tency of the antacids, as shown in Table 131, with the results of *in vivo* dies in Table 134, it will be found that the *in vivo* order of potency may predicted from the theoretic or calculated order of potency.

Antacid Material: Relative Potency *in Vivo*

Nonmedicinal Protein Foods. *In vivo* milk and cream in the usual nount administered hourly has been found in most cases to yield what ne would call "inadequate neutralization" (34–37). In a detailed estigation, Kirsner and Palmer (38) found that 90 cc. of milk and cream lf milk and half 20 per cent cream) did not control the "free acidity" the gastric contents. The free acid rose gradually to 40 C.U. or mEq. by 0 or 3:00 P.M., and rose even higher after 7:30 P.M. On referring to ble 133, it will be noted that the milk and cream schedule does not trol the free acidity of the gastric contents quite as well as three meals a general diet. So, the favorable effect of milk and cream on the healing peptic ulcer as compared to a general diet is probably due to the oothness and blandness of the milk and cream.

Powdered Whole Milk. Triple strength milk made from powdered whole lk and given in 90 cc. amounts hourly is considerably more effective in trolling free acidity than whole milk (Table 133). This is due to the ffer effect of the greater amount of protein and perhaps to the inhibitory ct of the greater amount of fat (11 per cent).

Table 133

NEUTRALIZATION OR BUFFERING OF "FREE ACIDITY" *in Vivo* OF VARIOUS MATERIALS, SAMPLES OF GASTRIC CONTENTS BEING TAKEN EVERY 30 MINUTES*

Regimen	*A.M. to P.M. Period of Day Studied*	*Number of Experiments*	*C.U.† or pH of Gastric Contents*		*Remarks*
			Average	*Range*	
Effect of Diet					
General diet; three meals	7– 5	17	pH 1.8	pH 1.3– 2.5	Evening meal not included
90 cc. milk and cream hourly	7– 5	20	pH 1.5	pH 1.1– 1.7	" " " "
90 cc. whole milk hourly	7–10	20	C.U. 55	C.U. 30 –70	Evening rise in acidity
90 cc. milk and cream hourly	7–10	19	C.U. 45	C.U. 30 –70	" " " "
90 cc. 18 per cent cream hourly	7–10	19	C.U. 37	C.U. 30 –65	" " " "
90 cc. 30 per cent cream hourly	7–10	10	C.U. 32	C.U. 30 –52	" " " "
90 cc. double powdered milk hourly	7–10	14	C.U. 27	C.U. 12 –70	" " " "
90 cc. triple powdered milk hourly	7–10	14	C.U. 20	C.U. 5 –70	" " " "
3000 cc. milk and cream with 10 Gm. per l. of $NaHCO_3$ by 24 hr. drip	24-hour drip	35	C.U. 10	C.U. 5 –25	Very slight evening rise in acidity
Effect of $NaHCO_3 + CaCO_3$					
90 cc. milk and cream hourly	7.5–7.5	55	C.U. 35	C.U. 22 –42	Evening rise in acidity
2 Gm. each $NaHCO_3$ hourly	7.5–7.5	16	C.U. 10	C.U. 5 –17	Evening acidity not followed
90 cc. milk and cream, 2 Gm. each $NaHCO_3$, $CaCO_3$ hourly	7.5–7.5	58	C.U. 12	C.U. 5 –15	Evening rise in acidity
Effect of Atropine					
90 cc. milk and cream hourly; 2 Gm. each $NaHCO_3$, $CaCO_3$, 1 mg. atropine sulf. at 6 and 10 P.M.	7.5–7.5	10	C.U. 5	C.U. 0 –10	Moderate evening rise
90 cc. milk and cream hourly; 1 mg. atropine sulf. at 8.5, 10.5, 1.5, and 3.5 o'clock	7 5	17	pH 1.7	pH 0.9 2.8	Evening acidity not followed

Table 133 (Continued)

Regimen	*A.M. to P.M. Period of Day Studied*	*Number of Experiments*	*C.U.† or pH of Gastric Contents*		*Remarks*
			Average	*Range*	
Effect of Atropine					
90 cc. milk and cream hourly; 4 Gm. $CaCO_3$ hourly; 1 mg. atropine sulf. at 8.5, 10.5, 1.5, and 3.5 o'clock	7–5	15	pH 5.3	pH 4.7– 5.8	Evening acidity not followed
90 cc. milk and cream hourly; 4 Gm. $CaCO_3$, hourly; no atropine	7–5	26	pH 4.9	pH 3.7– 5.8	" " " "
Tribasic Phosphates					
90 cc. milk and cream hourly; 2 Gm. tribasic $Ca_3(PO_4)_2$ hourly	7–5	20	pH 2.4	pH 1.6– 3.3	" " " "
90 cc. milk and cream hourly; 2 Gm. tribasic $Mg_3(PO_4)_2$ hourly	7–5	19	pH 2.8	pH 1.5– 4.2	" " " "
Magnesium Trisilicate					
90 cc. milk and cream hourly; 2 Gm. magnesium trisilicate hourly	7–5	18	pH 2.3	pH 1.4– 3.3	" " " "
$MgCO_3$ and $CaCO_3$					
90 cc. milk and cream hourly; 2 Gm. $MgCO_3$ hourly	7–5	20	pH 4.6	pH 2.7– 6.5	" " " "
90 cc. milk and cream hourly; 2 Gm. $CaCO_3$ hourly	7–5	15	pH 3.9	pH 2.4– 5.4	" " " "
90 cc. milk and cream hourly; 0.7 Gm. $CaCO_3$ + 0.5 Gm. $MgCO_3$ hourly	7–5	21	pH 4.1	pH 2.4– 5.8	" " " "
AL $(OH)_3$					
90 cc. milk and cream hourly; 4 cc. $Al(OH)_3$ gel hourly	7–5	25	pH 1.8	pH 1.2– 2.4	" " " "
90 cc. milk and cream hourly; 16 cc. $Al(OH)_3$ gel hourly	7–5	22	pH 2.2	pH 1.6– 2.8	" " " "
90 cc. milk and cream hourly; 30 cc. $Al(OH)_3$ gel hourly	7–5	22	pH 2.7	pH 2.3– 3.4	" " " "

* References 38 and 79.

† "Free acidity," using Töpfer's reagent, pH 4.0.

Data of the type in this table are not available for protein hydrolysate or synthetic resins.

Protein Hydrolysate and Protein Foods. Data similar to that provided for milk and milk powder are not available for protein hydrolysate and protein foods. However, unless protein hydrolysate should stimulate gastric secretion more than powdered milk, it should buffer acid slightly better *in vivo* than powdered milk because it has more free amino or basic groups available. Milk is deficient particularly in Vitamin C and iron, both of which contribute indirectly to healing. The deficiencies must be made up and every "strict diet" inspected for deficiencies (39). Another disadvantage is that some persons manifest a "food sensitivity" to milk; it was found to be the offender in 7 per cent of 500 cases of "food sensitivity" (40).

Protein Hydrolysates. A milk and cream diet may be deficient in protein, and the patient may be in negative nitrogen balance. In addition, the level of serum protein and albumin in ulcer patients may be lower than normal (41). This predisposes to traumatic edema in the case of an operation, to poor healing, and to ulcer formation (see p. 309). So it is appropriate to add protein to the milk and cream for its nutritional and "antacid" values.

Various protein hydrolysates given with milk or dextrimaltose have a good buffer or "antacid" capacity (42–45). When given in adequate amounts, positive nitrogen balance occurs (42, 46).

Protein Foods. Other protein foods such as casein in various forms, soya bean, milk powder, soft boiled eggs, and gelatin do not contain natural gastric secretagogues and may be used to maintain the protein intake at a high level (80 to 120 Gm.). Though gelatin is not a complete protein, it may be used with casein, which is a complete protein. Undigested proteins do not have as much immediate acid buffering effect as digested protein (protein hydrolysate). In some instances, protein hydrolysates are to be recommended, but as a rule the undigested protein food is apparently adequate and is preferred by the patient (47).

Medicinal Antacids: Relative Potency *in Vivo.* We are indebted principally to Kirsner and Palmer (38, 48) for studying the relative potency *in vivo* of medicinal antacids in combination with milk and cream. After determining the "free acidity" either in clinical units or in terms of pH (see Table 130), they usually gave 90 cc. milk and cream with the antacid, on the hour, removing a sample of contents just before the hourly feeding. This was done from 7 A.M. to either 5 or 10 P.M. Usually 15 or more tests were made with each antacid.

The results are shown in Table 133 and are summarized in Table 134.

A number of significant points come from these data. *First*, an increase of fat, as cream, decreases the average free acidity. This we might anticipate on the basis of the action of the enterogastrone mechanism. *Second*, triple strength milk, which has an augmented buffering property and fat

ontent, as compared to normal whole milk, decreases the average free cidity. *Third*, as might be anticipated, a 24 hour round-the-clock control f free acidity is possible by use of the Winkelstein drip technique. *Fourth*, uring the period of feeding and medication, effective control of "free cidity" may be obtained on the average by the first four methods listed n Table 134. *Fifth*, a combination of calcium carbonate (constipating) and nagnesium carbonate (laxative) appears to be the best antacid if com- lete or almost complete neutralization of "free acidity" is desired without

Table 134

In Vivo Neutralizing Value of Various Antacids Taken Hourly with 90 cc. Milk and Cream in Order of Greatest to Least Potency

1.	4 Gm. $CaCO_3$ with 1 mg. atropine sulfate at 8:30 and 10:30 A.M. and 1:30 and 3:30 P.M.
2.	4 Gm. $CaCO_3$ without atropine
3.	2 Gm. $MgCO_3$
4.	0.7 Gm. of $CaCO_3$ with 0.5 Gm. of $MgCO_3$
5.	2 Gm. $CaCO_3$
6.	Winkelstein 24 hr. drip 3000 cc. milk and cream with 30 Gm. $NaCO_3$
7.	2 Gm. each of $NaHCO_3$ and $CaCO_3$
8.	2 Gm. tribasic magnesium phosphate
9.	30 cc. of $Al(OH)_3$ gel
10.	2 Gm. tribasic calcium phosphate
11.	2 Gm. magnesium trisilicate
12.	Triple strength powdered milk

he complication of constipation or diarrhea. The appropriate dose of nagnesium carbonate must be determined for each patient because of the ariation in its laxative effect. *Sixth*, in addition, Wosika and Emery (49) ave found that no significant difference in neutralization of "free cidity" occurs when the antacid is given on the hour with the feeding or n the half hour between the feedings.

Before discussing the relative merits of the various antacids, it is best o discuss the various therapeutic regimens in which they are used.

Various Therapeutic Regimens

Sippy Regimen

Sippy (10, 50) was the first to introduce a comprehensive program for he management of peptic ulcer. It was designed to decrease the mechan-

ical effect of "rough" food and to maintain "an accurate neutralization of all free hydrochloric acid during the time that food and its accompanying secretion are present in the stomach." Late evening secretion or distress associated with "night secretion" was controlled by therapeutic aspiration at bed-time or later if required. The patient was hospitalized for from two weeks to two months to insure rest and to render the program of education relative to how to eat and live easier and more effective.

The routine or standard regimen, though slightly modified from the original Sippy, may be outlined as follows:

1. "First Day Sippy." This is the basic "milk and cream and powder with bed-time aspiration schedule."

a. 90 cc. of half-and-half whole milk and 20 per cent cream on the hour from 7 A.M. to 7 P.M.

b. Powder No. I (0.65, 1.3, or 2 Gm. calcium carbonate plus 2 Gm. of sodium bicarbonate) to be taken on the half hour or the hour with the milk and cream. The amount of calcium carbonate required is determined by sampling the gastric contents for "free acidity" just before a feeding at the "bed-time aspiration." It is best to start with the 2 Gm. of $CaCO_3$ and reduce, if indicated. Powder No. II (0.65 Gm. each of magnesium oxide (MgO, heavy) and sodium bicarbonate) is given to regulate the bowel movements. In some patients, none and in others six of these powders are required. They are substituted for or added to Powder No. I as indicated.

c. The milk and cream is stopped at 7:00 P.M. but a powder is taken at 8 and 9 P.M. and the stomach aspirated at 9:30 P.M. and later if indicated.

d. Most patients like the milk and cream after getting started on it. But some patients cannot tolerate the cream; then whole milk, skim milk, evaporated milk, or milk powder is substituted; also, chocolate sauce, malted powders, or ice cream may be added to the milk.

The milk (45 cc.) and 20 per cent cream (45 cc.) for 13 feedings (7 A.M. to 7 P.M.) provides 1,528 calories, the basic foodstuffs being distributed as follows: CHO, 58 Gm.; protein, 36 Gm.; fat, 128 Gm.

2. Schedule of "Additional Feedings." The "basic milk and cream and powder with bed-time aspiration" schedule is continued for months. The aspirations are discontinued when the volume of the 9:30 or 10:00 P.M. aspiration does not exceed 100 to 150 cc.

Additional feedings are started on the second or third day and are increased during the first two weeks so that on the seventh day the patient is receiving four additional feedings and on the eleventh or fourteenth day six additional feedings. These feedings are generally added to the 90 cc.

ilk and cream and powder or in some cases, as indicated, substituted or the 90 cc. of milk and cream.

The food to be used for the first, second, or third additional feedings ay be chosen from the following list, enough NaCl being added to yield a aily intake of 10 Gm.:

Boiled rice
Rice cooked with milk
Farina
Cream of wheat
Strained oatmeal
Soft cooked egg
Poached egg
Custards
Whipped cream
Blanc mange
Jello or junket
Chocolate sauce
Malt powder syrup
Milk powder
Ice cream
Protein hydrolysate
Bavarian cream
Cottage cheese
Spanish cream
Lemon sponge
Grape sponge
Bread pudding
Cornstarch or tapioca pudding

The following foods may be added to those in the above list when the eedings are increased to four, five, or six daily:

Soft omelet
Soft scrambled eggs
Jelly
Dry toast
Milk toast
Butter
Angel cake
Sponge cake
Plain cake
Wafers, free of roughage
Strained cream soup
of celery
of carrot
of asparagus
of pea
of potato
of spinach
of tomato

The milk and cream diet plus three additional feedings provides oughly 2,150 calories, the basic foodstuffs being distributed as follows: HO, 186 Gm.; protein, 70 Gm.; fat, 190 Gm.

3. "Three Meal Schedule." The "three meal schedule" is generally tarted during the third week. *This should depend on the extent to which the rater has filled in or the gastric retention and/or duodenal deformity has improved.*

The "basic milk and cream and powder with bed-time aspiration" chedule is continued, the only change being that three larger meals are aten as breakfast, dinner, and supper. The dietary items for the three neals are selected from the following list:

Breakfast

Orange juice
Baked apple (no skin)
Apple sauce
Juice or purée of canned or cooked peaches, pears, prunes, apricot, banana, tomato, boiled cereals, eggs (cooked soft), toast, butter, jelly, chocolate, Sanka, half cup of coffee or tea with cream and sugar

Noon or Evening Meal

Soups: any vegetable strained and creamed
Bread: (toast preferable) and butter as desired
Meats: minced beef, lamb, veal, or mutton; all meats, chicken, fowl, and roasts should be thoroughly chewed, if not minced; broiled meats, if chewed well, are permitted after three or four months
Vegetables: any, if cooked and puréed, or well chewed
Cooked starch foods: any type, such as potatoes, spaghetti, noodles
Dessert: ice cream, custards, puddings (not spiced), cottage and cream cheese, wafers, light dry cakes

When the patient returns to work, the noon meal should be relatively light. Some patients do much better if the evening meal is light, and a bed-time snack of milk with or without a malt preparation and crackers or wafers, or a custard with milk and cream is taken, or milk toast, or cottage cheese, or cream cheese on crackers, or melba toast.

4. Instructions for the Ulcer Patient. When the patient is in the hospital, instructions regarding peptic ulcer, its excitatory causes, and the reasons and objectives of the treatment being followed are given. When the patient is dismissed, written instructions with the above dietary list are given the patient. In these instructions, Dr. Sippy made the following points: (a) Ulcer heals slowly and may return; hence the *patient must remain on the management for 12 or 18 months*, when it will be further modified. (b) The patient should return regularly as instructed, so that the progress may be observed and supervised. (c) All foods must be cooked soft or puréed, or well chewed, and highly seasoned foods avoided. (d) A day's supply of the milk and cream mixture can be put up in a thermos bottle and should be taken regularly with the powders. (e) The volume of the bed-time aspirate and acidity is to be recorded nightly and reported to the physician at the patient's next visit. (f) A streak of blood has no significance. If the stools become black or tarry or blood is vomited, or if sudden severe pain in the abdomen occurs, the patient should call the physician at once. (g) If distaste for milk, headache, a feeling of sickness,

nausea occurs, the patient should stop taking the powders and call the physician.

5. Sippy also used bismuth subcarbonate, which has been used for many years. It tends to check the diarrhea caused by the magnesium salts. It is believed to have a soothing action like 25 Gm. of barium sulfate taken four times a day. These heavy powders do not usually coat the ulcer or fill the crater, though at times they may (51). Bismuth has the disadvantage, like iron, of darkening the stools and of rendering the recognition of slight melena difficult.

Other Regimens

The basic Sippy program has been modified in many ways. None of the modifications depart far from the dietary regimen. A few of these will be given for the purpose of orienting the reader for a subsequent discussion of the effectiveness of the various regimens.

Regimen A: Frequent Feedings Starting with Milk and Cream. The patient is started on the 90 cc. of milk and cream every hour up to 9 P.M. Mineral oil (8 to 16 cc.) or some vegetable mucilage is taken before retiring for constipation, if necessary. In some cases, laxative magnesia powder, with or without belladonna and kaolin, is given if necessary, and belladonna and phenobarbital are given if necessary. After four days, the diet is increased if progress is satisfactory, as in the case of the Sippy regimen. After six weeks, if the crater is filled, a "bland six meal diet" consisting of the foods in Sippy's "three meal schedule" is instituted. Practically the same diet is continued indefinitely.

Regimen B: Frequent Feedings Starting with Soft, Bland Diet. The patient is placed on six feedings a day consisting of milk, cream, and the bland foods used in the second week Sippy schedule and then after evidence of "healing" has occurred, six meals of the foods in Sippy's "three meal schedule" are allowed.

The "Rest Cure" or "Fasting Treatment." This was introduced in 1876 by Leube (52) and was used quite extensively until 1920 (53). It was modified in many ways. The last version was called the "physiologic rest" regimen (54). It may be outlined as follows: (a) Rest in bed for one to three weeks; (b) rest of the affected part by allowing no food or drink by mouth for three to seven days, chewing paraffin being encouraged to keep the mouth moist; (c) application of warm, moist compresses to the epigastrium; (d) rectal alimentation of solution of 30 cc. of ethyl alcohol, 30 Gm. of glucose in 240 cc. of normal saline solution, which is given four times daily; (e) oral feeding is started on the third to fifth day and consists of frequent feedings of liquid gruel, Dextrimaltose, and thin creamed vegetable soup, and 0.3 to 0.6 Gm. of magnesium oxide every two or three

hours, milk being used sparingly. Tincture of belladonna or opium is given for pain when indicated.

Items of Management Other than Reduction of Acidity

Apparent Importance of Rest

Rest, both mental and physical, is generally agreed to be valuable in the management of the exacerbation of peptic ulcer. This does not imply that the patient must be confined to a hospital. Rest may be obtained at home if the domestic environment is favorable. The reassurance that comes from a regular therapeutic schedule, a new therapy, or a modification of an old therapy gives even the ambulatory patient who continues to work some rest, since release from apprehension and fears restores emotional equilibrium. It is important to understand the patient sympathetically and restore emotional calm. It is much better to do this without resorting to sedatives.

Physical rest and, more important, muscular relaxation appear to be important. Muscular relaxation may be derived from a vacation in pleasant surroundings and frequently where enough muscular exercise is taken to cause a mild, comfortable fatigue. Hospitalization will assure physical rest, but not necessarily emotional rest. It should be conducive to both, however. It is the best place to teach the ulcer patient about his disease and the importance of adhering carefully to a program of "curative" as well as prophylactic therapy.

The amount of bed-rest recommended varies from a few days to a week. Certainly *a penetrating ulcer should be treated with bed-rest until the symptoms and roentgenologic findings show the absence of a penetrating lesion.* The duration of hospitalization, among its advocates, varies from two to eight weeks. As Palmer has stated, "usually it is best to compromise between that which is desirable and that which is necessary." There is certainly a group of patients that need not be hospitalized. As will be seen later, it appears that a definite schedule for eating and living seems to be the most important item in the management of peptic ulcer patients as a group omitting those with penetrating lesions and complications.

Apparent Importance of Diet

It should be pointed out that in former years and as late as 1925, peptic ulcers apparently healed under the regimen referred to as the "rest cure" or "fasting treatment" (53). Under this treatment, the patient received little food during the first week (54). However, *we have no roentgenologic data which renders it possible to compare the rate of healing under the regimen of fasting and of frequent feeding.*

If frequent feeding is employed, and we believe it should be, it has been well demonstrated experimentally and clinically that the diet should be soft and semifluid. In addition, it is rational to believe that the diet should be nutritious and contain items conducive to healing.

Protein of good quality is conducive to healing as well as to buffering of acid. The proteins of milk are of the highest quality and it is rational to use milk and to add protein in the form of milk powder to milk. The Sippy diet of milk and cream contains only 35 Gm. of protein; even with the six additional feedings it contains only 85 Gm. The diet should probably contain 100 Gm. of high quality protein. Of course, protein stimulates acid secretion. This is true, though to a variable extent, of all foods and liquids. Fats and sugars in adequate concentration by weight or volume (10 per cent or more) inhibit gastric secretion and motility. So, high protein milk (addition of milk powder or hydrolysate) with cream would appear to be a rational food to use.

If it is desirable to reduce the weight of the patient or if the cream is not well tolerated, a high protein skimmed milk would be next in choice. If milk is not tolerated, which is rarely the case since intolerance may usually be overcome, then a protein hydrolysate in Dextrimaltose or chocolate syrup may be used. Sometimes milk is well tolerated after cooking it slightly.

A patient on the Sippy diet usually loses weight during the first week, returns to the initial pretreatment weight the second week, and then continues to gain unless the caloric intake is restricted.

With the exception of Vitamin C, the vitamin intake is adequate even during the first week on the Sippy diet. The intake of vitamin C becomes adequate when the fruits are added. It would not be amiss to give 75 mg. of ascorbic acid daily until the patient is receiving the "three meal diet." The fact that an alkaline reaction inactivates Vitamin C should be taken into consideration as regards the best time and route of administration. The level of vitamin C in the blood and urine is lower in peptic ulcer patients than normal subjects (55) and the alkalinity of the blood deleteriously affects the metabolism of the vitamin (56).

In some patients, iron other than that in the food is needed, and it should be remembered that it is not so well absorbed from an alkaline intestine. Small doses of iron given hourly are reported to be better absorbed than when the total is given as one dose (57); the small doses are less likely to irritate. So, 60 mg. of ferrous sulfate could be taken with each feeding, or 60 mg. of ferric ammonium citrate may be given daily intramuscularly.

Olive oil has been used in many ulcer managements because it inhibits gastric secretion, tends to be laxative, and has an emollient action. Fifteen

cc. were given before three or four of the frequent feedings used by Hurst (58), who states that many ulcer patients like to take it and there is no good reason why more than 15 cc. should be given. Some have used up to 60 cc. three or four times daily.

Antispasmodics

The potential value of an antispasmodic in the peptic ulcer patient may frequently be demonstrated by injecting 5 or 10 mg. of dibutoline (Merck) subcutaneously while taking the history if the patient has any distress or pain, particularly if the distress has the quality of tension or gnawing. The same is true if 1 mg. of atropine sulfate is given intravenously. We have seen patients with distress after three or four days on a strict Sippy regimen in whom the distress was abolished by one or several subcutaneous injections of 1 mg. of atropine sulfate, and after the relief the Sippy regimen was adequate to prevent the return of the distress. Symptomatically, the rather prompt relief or the control of the distress, when it occurs, is desirable, but there are no data showing that atropine or dibutoline speeds the rate of "filling in" the crater. Nevertheless, there is no doubt that atropine sulfate in doses adequate to cause some xerostomia decreases gastric tone and the volume of gastric secretion, and when given every two or three hours will render it easier to neutralize the "free acidity" of the gastric contents on an hourly milk and cream and alkali powder diet (Table 133).

Sedatives

A sedative such as phenobarbital is frequently used in the early management of peptic ulcer patients. It is sometimes combined with atropine or belladonna. Sedatives should be used only when the necessary rest and relaxation cannot be secured by more hygienic means and then only temporarily as a bridge.

Therapeutic Aspiration of the Stomach

Symptomatic Aspiration. Symptomatic aspiration of the stomach at bed-time or between 12 midnight and 3 A.M. is not infrequently necessary to provide relief from pain. This is particularly true in the presence of retention, definite hypersecretion of acid, and penetrating lesions.

Routine Aspiration. Routine aspiration at bed-time has the following arguments in its support: (a) It is a check on adequate neutralization performed 30 minutes after the last powder. (b) Before retiring the stomach is emptied of any secretogogues which may still be present and tend to induce an interdigestive phase of secretion. (c) It is a good disciplinary procedure, especially since practically all patients learn quickly how to make the aspiration without displeasure.

In the case of excessive night secretion, aspiration at midnight for the first week or two, especially in the presence of hypersecretion, will decrease the exposure of the ulcer to acid. At times, it is advisable to give 1 mg. atropine sulfate or 10 mg. dibutoline at 10 P.M. before retiring, along with 4 Gm. of $CaCO_3$. In difficult cases, milk and cream with powders, or a continuous drip is required.

It must be kept in mind that aspiration, like vomiting, removes Cl^- from the body, and hence it predisposes to alkalosis unless the Cl^- is replaced with NaCl in the diet.

Clinical Use of Various Antacids and Miscellaneous Products

Alkalis. Sodium bicarbonate, calcium carbonate, and magnesium oxide have been most widely used because they usually provide prompt relief of symptoms, are usually well tolerated, and are inexpensive.

Sodium Bicarbonate. Given in large doses, this is most likely to cause alkalosis and hence some believe it should not be used. For this reason, and because it is not as effective as calcium carbonate in neutralizing acid (38, 59), mixtures of the two alkalies have been extensively used. In 1927, the merits of *calcium carbonate* as an antacid were indicated by Lovenhart and Crandall (60). Since then, it has been employed alone in place of mixtures of sodium bicarbonate and calcium carbonate, and its use is quite popular today. Excessive doses will cause alkalosis occasionally (*vide infra*). It tends to produce constipation in a number of patients and the formation of fecoliths and fecal impaction has been described (61, 62). Alkalined tablets of powdered milk have been used and the neutralizing and buffering action studied. They serve only as a convenient way to administer an antacid and food. Their use is more rational than tablets of the aluminum salts and other antacids where particle size is an important factor in the rate of neutralization.

Magnesium Oxide. This has been and still is used widely because it is a good antacid and counteracts the constipating effect of calcium carbonate. The widespread practice of "titrating" the laxative effect of the magnesium ion, as the oxide or carbonate, against the constipating effect of the calcium ion is criticized by several authors (12, 63, 64) because of the frequency of "cathartic colitis." However, the large majority of patients manifest no ill effect from a small but therapeutically effective dose of magnesium oxide or carbonate, and "cathartic colitis" may be avoided by observing the patient carefully. The *phosphates of calcium and magnesium* were introduced as antacids by Greenwald (65) in 1923. They have been used clinically with "satisfactory" results (14, 66–68). In some patients, it has been necessary to revert to calcium carbonate for the con-

trol of symptoms. In a study of six patients, it has been found that the tribasic phosphates cause no change in blood and urine chemistry (68).

Aluminum Hydroxide Gel. Aluminum hydroxide gel (U.S.P. XIII) is widely used today in the management of peptic ulcer. It neutralizes acid slowly on the basis of a simple chemical reaction (69, 70). Since its properties are such that it cannot neutralize acid beyond a pH of 3.5 or 4.0, it is not as good a neutralizing substance as sodium bicarbonate, calcium carbonate, or magnesium oxide, but is approximately as good as the tribasic phosphates and magnesium trisilicate (15, 71–74). When used instead of alkaline powders with 90 cc. of milk and cream and 16 cc. of the gel or suspension, an average pH of 2.2 may be maintained (Table 133), (37, 38, 75). Aluminum hydroxide powder is less effective than the gel or suspension (76) and there is a variation in effectiveness due to a variation in particle size.

Aluminum hydroxide gel has no effect on the gastric mucosa or on gastric motility and emptying (77). It causes no significant change in gastric secretion (76, 78–84). The absorption of aluminum is very slight (76, 80, 85, 86) and no change in acid-base balance (76, 80, 87, 88) or renal function (87, 88) occurs. It may cause alterations in the absorption of phosphorus (2, 26, 89) which occur significantly only when there is a deficiency of pancreatic juice or a relatively low phosphorus intake in the diet. The usual ulcer management, because of its content of milk, contains adequate phosphorus. The first sign of a phosphorus deficiency is a loss of appetite. Iron absorption in the anemic rat is reduced by aluminum hydroxide. This is also true of calcium carbonate (90). The absorption of Vitamins A and C, amino acids, glucose, and fat is not significantly impaired (91–93).

Clinically, the side reactions to aluminum hydroxide gel are few. Constipation is common and may be severe in patients confined to bed and given a low residue diet (94, 95); it is usually controlled easily by the use of mineral oil. Magnesium hydroxide suspended in aluminum hydroxide gel has been used with satisfactory results (96).

"Nonreactive Alumina" Preparations. "Nonreactive alumina" preparations with practically no chemical activity have been used only in a few patients. In two studies, in which good supportive therapy (frequent feedings of a smooth, bland diet) was used, no clinical difference between "nonreactive" and "reactive" alumina preparations was observed (97, 98).

Aluminum Phosphate Gel. This substance, which is frequently used clinically, was designed (2) to avoid the interference with phosphorus absorption caused by the hydroxide. In Mann-Williamson dogs in which there is a relative deficiency of pancreatic digestion, it was found that

aluminum hydroxide caused a loss of appetite, due to a phosphorus deficiency, and did not prevent the development of a jejunal ulcer. The phosphate gel, however, was very effective in preventing ulcer. It was pointed out that this difference should not be interpreted as evidence of superiority of phosphate over the hydroxide in man except in patients with an anastomotic ulcer, diarrhea, a relatively low phosphorus intake (little milk), or a pancreatic deficiency (2).

It has been found, on using the continuous intragastric drip, that the pH of the gastric contents averaged 4.0 with aluminum phosphate, which was higher than with the hydroxide. This was due to the fact that the phosphate can be used undiluted in the drip apparatus.

The phosphate gel causes no change in acid-base balance (89) or in calcium-phosphorus metabolism (89, 99), and no disturbance in the absorption of iron (90), Vitamins A and C, amino acids, glucose, and neutral fat (92, 93). Constipation tends to occur (2, 100) but less so than with the hydroxide (2, 99).

Satisfactory symptomatic response and x-ray evidence of healing have been reported when given intermittently with a smooth, bland diet (2, 99, 100). Winkelstein and his associates (122–124), who have had extensive experience with the drip method, prefer aluminum phosphate for that method of therapy.

Magnesium Trisilicate. Magnesium trisilicate in adequate doses has been shown to have some neutralizing effect *in vivo* (18, 21, 37, 101, 102) though 2.0 Gm. doses given hourly with milk and cream have only a slight effect, about equal to 16 cc. of aluminum hydroxide (Table 133) (48). The powder is more effective than the tablets (38).

This compound does not affect plasma bicarbonate or pH or nitrogen partition of the urine (19, 23). It has little influence on iron absorption (90). Occasional diarrhea, easily counteracted with some calcium carbonate, is the only side reaction noted.

Though the use of this compound has been attended with satisfactory clinical results (19, 21, 101–105), it cannot be said to be superior to calcium carbonate or the alumina gels.

Synthetic Resins. These have only been introduced recently and not much *in vivo* study has been conducted. A large dose is required to exert much effect on the pH of the gastric contents (27). Those studied have not been toxic (27–29). In more than 100 patients with peptic ulcer, the resin gave satisfactory relief from pain, diarrhea due to bulk being observed in only two cases (27, 106).

Gastric Mucin. This was introduced because it is an emollient and normally a protective substance against chemical and mechanical irritation, and because it was hypothetically believed that a relative deficiency

in mucous secretion might exist in the patient with peptic ulcer. The initial gastric mucin prepared had an appreciable acid-combining power (30, 32, 33) due to its content of peptones. *In vivo*, however, this was not very important (35, 107), and the peptone stimulated gastric secretion to some extent (108); so much of the peptone was removed. In experimental animals, gastric mucin was found to be of value in the prevention of peptic ulcer (33, 109, 110).

The clinical results, regardless of the unpalatability of the product, were favorable and a reasonable percentage of patients who failed to improve on orthodox antacid management manifested symptomatic relief and objective improvement (30, 31, 107, 111). It is in the management of such patients that gastric mucin has continued to be used.

Okrin. This vegetable mucilage, made from the pod of the okra plant, has been used clinically as an emollient in the place of gastric mucin. Symptomatic relief was obtained in some patients (112–114). Its use was not continued because its adjuvant action was not as favorable as gastric mucin and other adjuvants in the management of peptic ulcer.

Pectin. Pectin has also been employed (115).

Protein Hydrolysates. These have been used in patients with peptic ulcer with symptomatic relief and disappearance of the crater in most cases (42, 43, 46, 116). Using a high protein diet with a supplement of gelatin, equally satisfactory results have been obtained (45).

Duodenal and Jejunal Feeding. This procedure was introduced in 1910 by Einhorn (117) and was prompted by the idea of placing the stomach and duodenal bulb at rest. A mixture of milk, eggs, and sugar, which has been variously modified by others, was slowly introduced into the duodenum by a drip at two hour intervals, or by continuous drip, usually from 8 A.M. to 8 P.M. The pabulum must be administered slowly to prevent nausea, especially early in the course of the therapy. The treatment is continued for one to three weeks.

Ulcer distress usually disappears within 48 hours. Einhorn (118) reported that all but four of 300 patients responded satisfactorily to the treatment. This was confirmed by others (119, 120) and for a period the therapy was used quite widely in the United States.

Bockus (121) introduced the tube into the jejunum to decrease the extent of regurgitation of the pabulum to the duodenal bulb and stomach. He also gave *alkalis* orally to neutralize the gastric acid resulting from the intestinal stimulation of gastric secretion. He reported disappearance of the x-ray evidence of ulcer in seven of nine patients within one month after the two week period of jejunal feeding.

A soft, bland diet or the Sippy dietary schedule is followed after the cessation of duodenal or jejunal feeding.

Continuous Intragastric Drip. This therapy was introduced in 1932 by Winkelstein as a result of his studies on gastric secretion of ulcer patients during the night. He believed it was important to control the acidity during the night as well as the day. This could be done best and without nausea by introducing a fluid pabulum containing an antacid into the stomach continuously day and night for one, two, or three weeks, rendering the conditions as ideal as possible for the healing of the ulcer during the early stages. The introduction of the Penrose latex nasogastric tube by Woldman (13) in 1937 rendered the tube more tolerable. The gastric acidity was found to be well controlled during the day and night (122).

Very favorable clinical results have been reported to occur in complicated and refractory cases in which previous treatment had failed (123, 124).

If it is desirable to control acidity in the early stages of healing, which we believe is true of the penetrating ulcer, the ulcer causing much distress, and large ulcers, then this is the most logical treatment. With the tube in place, a sample of the gastric contents may be taken and titrated for "free acidity" or its pH determined at any time of the day or night.

Initially, 4 Gm. of sodium bicarbonate were dissolved in 1 qt. of milk and the mixture introduced into the stomach at a rate of 150 cc. per hour (about 40 drops per minute) or 3600 cc. in 24 hours for three weeks. Later, the duration of the 24 hour drip was decreased to three or four days for severe cases. In all cases but the severe, Winkelstein now gives three smooth, bland, "ulcer" meals three times daily "preceded with atropine and phenobarbital and followed with aluminum hydroxide or phosphate gel." The milk and soda drip is instituted "one hour after each meal and continued until one hour before the next meal and throughout the night." In the place of the milk and soda drip, a drip of aluminum hydroxide gel diluted three times with water, or four times with milk, or undiluted aluminum phosphate gel may be used. The resulting pH is essentially the same, namely, 3.5 to 4.0 (124). In some cases, a drip of milk alone is adequate to control free acidity. Also, some patients prefer not to have the tube removed and reinserted several times a day. An aluminum gel may be substituted entirely for the soda-milk, with mineral oil as indicated for constipation. Any antacid that can be suspended or dissolved may be used in the drip.

High Fat Diets. Various physicians increased the fat in the diet of the ulcer patient when it was found that a high fat meal (10 per cent or more by volume or weight) inhibits gastric secretion and motility for an hour or more. Olive oil, egg yolk, butter, and cream have been the fats used. Favorable clinical results, as might be expected from a soft, bland diet, have been reported (125, 126).

Powdered Duodenal Mucosa. A powdered extract of duodenal mucosa was given orally by Rivers, who believed the results warranted a closer study (127).

Parenteral Therapy. Many substances have been injected parenterally on the basis of the hypothesis that a nonspecific protein reaction would promote healing by stimulating the cells surrounding the ulcer and by decreasing gastric acidity. Holler (128, 129), in 1921, a period during which nonspecific protein therapy was being used for the treatment of many chronic diseases, reported favorable clinical results after a series of five to 10 injections of milk, dysentery vaccine, and autolysates of various organisms. It was observed that symptoms may be relieved without healing in some patients (130). A proprietary vegetable protein, called "novoprotein," on injection was reported to cause healing of an ulcer followed roentgenographically (131). "Aolan," a milk protein, was used rather widely at one time, but it apparently relieved symptoms without promoting healing (132). "Synodal," a lipoprotein with emetin, was also popular for a short time (133). Other proteins, which need not be mentioned, have been used. More recently, a polyvalent respiratory vaccine was used. This apparently caused the induction of a remission in 71 per cent of 33 ambulatory patients who had not responded to the usual ambulatory management (134).

Histidine monohydrochloride, known as "larostidin" or "stellidin," was quite popular for several years. Up to 24 injections were recommended. However, it has been reported that five or six injections and even injections of distilled water would give symptomatic relief or produce a remission in 55 per cent of patients (135). Pepsin has been injected with the idea that it would promote the formation of antipepsin and favorable results have been reported (136). A buffered citrate solution (137) and sodium benzoate (138) have been injected with alleged favorable results.

The use of parathyroid hormone, because an abnormal calcium level decreases gastric secretion, has been tried with satisfactory results (139). Pituitrin and the inhalation of posterior pituitary powder (141), insulin (140), and even histamine (142, 143) have been used, also with good results.

An extract of duodenal and gastric mucosa called Robuden has been claimed to be effective in inducing remissions in peptic ulcer (144). The actions of enterogastrone-containing preparations have been studied, but the authors have not claimed that the results observed are any better than those observed with a strict ulcer management (145).

The foregoing claims of good results are due to a failure to take into consideration the requirements for establishing the value of a therapy which have been outlined in the introduction to Part IV of this book.

Disadvantages of the Use of Alkalis

Alkalosis

This disadvantage of the use of alkalis was known to Sippy, though it was first emphasized by Hardt and Rivers (146) in 1923. When it occurs, it usually becomes manifest four to 10 days after the start of alkali therapy. The symptoms are a distaste for milk, cream, and alkalis, weakness, dizziness, headache, nausea, and vomiting. This may develop into nervousness, hyperactive reflexes, rarely tetany, clouding of the mentality, changes in personality, and, finally, coma. Alkalosis, however, is sometimes present in the absence of definite symptoms. Though symptoms are usually absent when the alkalosis is mild (serum CO_2, 31 to 40 mM/1, and pH 7.45 to 7.65), a strict relationship has not been found between the degree of chemical alkalosis and the severity of symptoms.

Alkalosis is defined as being present chemically when the serum CO_2 is above 30 mM/1, and the serum pH is above 7.45. For emphasis, it might be added, also when the serum chloride is below 95 mM/1, because the role of chloride has not been sufficiently appreciated in alkalosis due to excess ingestion of alkalis (Table 135).

Table 135

Normal Values and Values in Alkalosis for Serum CO_2, Serum pH, and Serum Chloride in Millimoles per Liter*

Degree of Alkalosis	*Serum Cl mM/1* Normal 95–105		*Serum CO_2 mM/1* Normal 22–30		*Serum pH* Normal 7.35–7.45	
	Range	*Average*	*Range*	*Average*	*Range*	*Average*
Mild	85.4–102.5	95.0	31.0–39.8	34.1	7.4 –7.65	7.51
Moderate	80.0– 91.1	88.0	35.9–43.3	39.2	7.5 –7.72	7.56
Severe	60.0– 90.4	77.0	38.6–62.1	48.0	7.52–7.73	7.61

* Kirsner (147).

The incidence of alkalosis, according to various authors in the literature, varies with their definition of the term, the time of withdrawal of blood samples, and the diligence with which deviations are sought. It also apparently depends on the age of the patient, the extent of hemorrhage, the loss of gastric juice (chloride) by vomiting or aspiration, and the presence of pre-existing renal disease (147). Kirsner found chemical alkalosis to be present in 30 per cent of 105 patients receiving 30 Gm. of calcium carbonate daily. Gatewood (62) found that two thirds of his patients on Sippy powders had a high plasma CO_2 content, or pH, or

both. Those who give small doses of alkalis have seen no cases of alkalosis, but others, using larger doses, have reported an incidence up to 30 per cent (62, 63, 148, 149).

The observations of Kirsner (147) show that the existence of alkalosis is not always correlated with the amount of sodium bicarbonate or calcium carbonate ingested. In view of the capacity of the normal kidney to excrete sodium bicarbonate in the presence of plenty of water (2.8 per cent) and the limited degree of calcium absorption by the intestine (maximum 3 Gm. per day), something other than the amounts of alkali ingested is involved.

Alkalosis associated with the ingestion of sodium bicarbonate is characterized by a rise in pH, CO_2 content, total base, and sodium, and a decrease in the chloride of the blood. Alkalosis from sodium bicarbonate should not develop if the kidneys are normal, water is taken in quantities sufficient to eliminate the base ingested, and enough chloride is ingested to maintain a chloride balance. For example, if a total of 10 l. of water (9.6 l. of urine) are taken daily with a total intake of 19.8 Gm. of sodium chloride (0.2 per cent in drinking water being required to prevent depletion of body sodium chloride), the tolerance for sodium bicarbonate would be 268 Gm. per day. If a total of only 3 l. of water (2.6 l. of urine) are taken daily with a total intake of 5.2 Gm. of sodium chloride, the tolerance for sodium bicarbonate without chemical alkalosis is only 73 Gm. per day.

Alkalosis associated with the ingestion of calcium carbonate is not so readily explained. It should not occur unless chloride is lost by vomiting, aspiration, or diarrhea. It should be prevented by the administration of adequate sodium chloride. It is possible, since calcium carbonate diverts phosphate from the urine to the feces, though generally in equivalent amounts, that in some patients excessive phosphate may be diverted from the blood into the feces. It is also possible that excessive chloride is lost in the feces by diarrhea or some unknown mechanism (147). The serum calcium is usually not increased and then only slightly (150, 151).

The evidence indicates, as might be expected, that impaired renal function predisposes to alkalosis (147, 149, 152, 153). However, it is well established that alkalosis may occur in the presence of normal kidneys (147, 150, 154). Renal function frequently diminishes during alkalosis, to become normal again on the clearance of the alkalosis (147). The literature dealing with the effect of long continued administration of alkalis on the kidney is controversial (89, 151, 155); it would appear, however, that the effect is slight when observed (147).

Treatment of Alkalosis. Alkalosis may be prevented in the absence of renal insufficiency by the administration of large amounts of water and 5 to 15 Gm. of sodium chloride daily (147, 151). After it has occurred to

the extent that severe symptoms appear, the alkalis should be stopped, the hypochloremia treated immediately with normal saline solution, and the dehydration, which is usually present, by 5 per cent glucose in 0.45 per cent saline. In mild or moderate cases of alkalosis, the dose of alkalis may be reduced or stopped, and 5 to 15 Gm. of sodium chloride with 5 to 6 l. of water administered daily.

Urinary Calculi

On reviewing 1,260 cases of urinary calculi, Kretschmer and Brown (156) found 1.2 per cent to have had previous alkali therapy. In 608 ulcer cases, 3.1 per cent had calculi before Sippy treatment and 4.9 per cent afterward. Though alkalis appear to favor the development of urinary calculi on the basis of this evidence, the difference could be due to chance, since it is not statistically significant. Eisele (157), however, studied 505 cases of urinary calculi and found 8.5 per cent to have had previous ulcer treatment and an additional 2.6 per cent who used alkalis for chronic gastrointestinal complaints. His conclusion was that in a total of 11.1 per cent of cases having calculi the use of alkaline powders was contributory. There are no apparent sampling errors to account for the differences between these series; differences in compilation of the data may be an explanation. Thus, the question of the etiologic significance of Sippy powders in urinary calculi remains open.

Rebound or Direct Stimulation of Gastric Secretion

It is generally conceded that the administration of alkalis (sodium bicarbonate and calcium carbonate) either stimulates gastric secretion or exerts a delayed stimulation, which is called rebound secretion. The general acceptance of this idea is based chiefly on two clinical observations. One of these is that in the ulcer patient who has been on the Sippy diet and powders, an aspiration at 11 or 12 P.M., or four or five hours after the last food, frequently yields a large volume (300 to 700 cc.) of strongly acid gastric contents. This is not reliable evidence because it is not known what the patient would produce in the aspiration if the diet without alkalis were given. The second observation is that calculations show that from 25 to 50 times more sodium bicarbonate is given hourly to an ulcer patient during the day (7 A.M. to 7 P.M.) than would be required to neutralize the amount of acid the stomach is believed to secrete (36). This may be due to the possibility that the stomach secretes more acid than anticipated and that considerable alkali is emptied from the stomach early after it is taken, as well as to the possibility that the alkali stimulates gastric secretion.

The literature contains many reports of experiments on the effect of alkalis on gastric secretion in the dog. Unfortunately, most of the articles provide results on only one or two experiments on one or two dogs. As might be expected, the results are conflicting. The more recent reports of Boyd and of Adams and of Clark are exceptions. Boyd found in the dog that the administration of up to 1 Gm. of $NaHCO_3$ per kilo body weight given after a meal stimulated the volume output of gastric secretion. Larger doses decreased the response, and the introduction of 1 per cent sodium bicarbonate solution into the stomach decreased or depressed gastric secretion (158). He also found that 5 per cent sodium bicarbonate solution placed in the stomach depressed the secretory response to histamine and that lower concentrations had no effect (159). Adams and Clark, using the dog, found a consistent increase in the volume output of gastric secretion when sodium bicarbonate or calcium carbonate was given with a test-meal, which did not occur when aluminum hydroxide was given (160). The data are not presented in the publications, so a statistical analysis of the significance of the differences between control and test responses cannot be made. However, it would appear from this work that when these alkalis are given in moderate amounts with a meal, they tend to stimulate, but when given in large amounts they depress. When given in aqueous solution on an empty stomach, they have no effect in moderate doses but depress in large doses. We believe that further work, in which the results are subjected to statistical analysis, is needed.

Several studies have been made in man; some of these are worthy of mention. Crohn (59) gave 2 to 4 Gm. of sodium bicarbonate 45 minutes after an oatmeal test-meal. Fifteen or 30 minutes later, the acidity of the gastric contents was higher than in the controls. This was interpreted as a "rebound" secretion or as a stimulation of gastric secretion. Bloomfield and Keefer (161) performed 24 tests on six subjects in which the alcohol test-meal was given with and without 1 to 2 Gm. of sodium bicarbonate and the indicator method for calculating the volume output of secretion was used. No evidence of stimulation of secretion was found. Lockwood and Chamberlin (126), using fractional analysis and an Ewald test-meal, also failed to observe a stimulation of secretion. It is believed that experiments conducted by the block method with milk and cream and with and without alkalis should be conducted for several hours. This would be comparable to the conditions under which alkalis are believed to stimulate and under which it has not been demonstrated that they do or do not. It should be done because the evidence from animals suggests that alkalis may augment the action of secretagogues in or produced from food.

Immediate Response to Strict Medical Therapy

The clinicians prior to 1910 obtained relief of symptoms in a large percentage of patients. Leube (162) and Lenhartz (163) reported complete relief of symptoms in approximately 90 per cent of patients. Nielsen (164) in 1923 reported complete relief in 93 per cent of patients who had had the symptoms for less than one year, in 63 per cent of patients who had had the symptoms for one to 10 years, and in only 40 per cent who had had the symptoms for over 10 years. Crohn (120) obtained complete relief in 86 per cent of patients using essentially the Sippy therapy. It is now well known that from 85 to 95 per cent of patients hospitalized and kept on strict management will obtain complete relief of their symptoms within two weeks.

Relative Effectiveness of Various Medical Therapies

Introduction

The data to be presented on this subject are best appreciated in historical perspective.

The first systematic therapy for peptic ulcer generally used was the "milk diet" of Cruveilhier (6). In 1876 Leube (52) introduced the "rest cure" (p. 893) on the theory that wounds heal best on bed-rest and rest of the affected part. Lenhartz (165) around 1900 advocated the view that peptic ulcer did not heal because of malnutrition. His regimen consisted of hourly feedings of milk and eggs and later raw beef and other soft foods were added. This therapy, like that of the "rest cure," was not liked by the patient. The theory of the "rest cure" and "gastric rest," however, caused the Leube treatment to be popular until Cannon and Carlson showed that the empty stomach is not completely at rest because it manifests hunger contractions and an interdigestive secretion. Sippy (1912) then introduced the concept of physical rest with complete neutralization of "free acidity" during the waking hours by the use of frequent feedings and alkalis and aspiration at night. Since then the patients have gotten along so well on a regimen employing frequent feedings that the preliminary period of fasting has practically disappeared from use since 1925.

The Sippy regimen was not completely accepted because of the hazard of alkalosis and the claim that the results do not justify the time and trouble the treatment, when strictly followed, requires. Unfortunately, taking something every half hour, or even every hour, or a continuous drip is disliked by even the most cooperative patients, and some patients will follow the regimen for only a short time. Thus, attempts to modify the

Sippy regimen have frequently been made. These modifications are in many instances claimed to relieve pain as early as the Sippy regimen. Relief of symptoms alone, however, is not a justifiable aim if it misleads the patient and physician into believing that healing is progressing or has occurred.

Hurst (58) argued that a change in diet every three or four days, as in the Sippy regimen, has "no rational basis." "If a certain diet is suitable for a certain day, it is absurd to assume that every ulcer . . . will have improved in twenty-four hours to just the degree which justifies the addition of an egg or a Zwieback to the diet." He used a soft diet with milk and olive oil hourly from 8 A.M. to 8 P.M. and alkalis and atropine.

It has also been argued frequently that the Sippy regimen does not neutralize completely and that there is no evidence showing that the complete neutralization of "free acidity" is necessary for healing. In fact, it is on the basis of this theory that the use of antacids which only partially neutralize have been used and claimed to be as effective as the strict Sippy regimen.

The question of the relative effectiveness of ulcer managements will not be determined by theory or debate; it will be answered only by the submission of evidence, first, regarding the time of disappearance of symptoms (pain and occult blood), and, *second*, the rate of disappearance of the crater.

In collecting evidence on these two topics, we have devoted no attention to the time of disappearance of occult blood because so many patients with an active ulcer and a crater do not manifest occult blood and because so many of the data are unreliable due to the type of diet used.

The time of filling in of the crater is the best criterion we now possess for following the rate of healing. Gastroscopic examination has been used in the case of gastric ulcer to check the reliability of roentgenologic methods. In about 75 per cent of the cases, it was found that the ulcer had been epithelialized soon after the disappearance of the crater.

Time of Disappearance of Symptoms

In Table 136, we have collected representative data on the time of disappearance of pain or distress on different ulcer managements.

Palmer (166) performed a controlled study in which the Sippy management was employed in 27 patients and in which 90 cc. of Liebig's meat extract was substituted for the powders in another 27 patients. The distress disappeared in an average of 2.8 days in the patients receiving the alkaline powders and in an average of 26.6 days in those receiving the meat extract. In those patients receiving alkaline powders, the longest duration of distress was 15 days.

These data clearly prove that alkaline powders are superior to meat

Table 136

DURATION OF PAIN AFTER START OF VARIOUS ULCER MANAGEMENTS (54)

Author	*Treatment*	*Number Cases*	*Average Duration Pain in Days*	*Remarks*
Smithies et al. (54)	Starvation "rest cure"	470	2.0	81 per cent in less than 3 days; 96 per cent in less than 4 days
Palmer* (166)	Hospitalization; milk, cream, Sippy powders	27	2.8	Acid test positive for 9.7 days
	Hospitalization; 90 cc. 10 per cent meat extract substituted for the powders	27	26.6	Acid test positive for 26.9 days
Dick & Eisele (12)	Hospitalization; milk and cream only	31	less than 7.0	"Less than one week;" one patient not relieved
Kenamore (46)	Milk, cream, Dextrimaltose	13	5.9	All patients hospitalized for 14 days; meals isocaloric
	Protein hydrolysate	18	2.6	
Co Tui et al. (42)	Hospitalization; protein hydrolysate and Dextrimaltose	26	2.0	In 100 per cent of patients
Hodges (43)	Hospitalization; protein hydrolysate and Dextrimaltose	26	4.4	In 88 per cent of cases
Cummins et al. (168)	Hospitalization; strict Sippy, belladonna and sedative	69	2–7	In 91 per cent of cases
Connelly (167)	Chiefly ambulatory; modified Sippy	20	2.0	In 85 per cent of cases
	AlOH	20	1.0	In 100 per cent of cases
Jones (250)	Ambulatory and hospitalized; soft diet plus AlOH	24	3 0	In 83 per cent of cases
Kyger et al. (251)	Chiefly ambulatory; six bland meals plus AlOH	62	2–3	In 89 per cent of cases
Emery et al. (79)	AlOH, milk and cream; some hospitalized	21	1.0	14 hospitalized, given drip; 7 ambulatory, given orally
Rutherford et al. (81)	AlOH, milk and cream; some hospitalized	28	1.0	18 hospitalized, given drip; 10 ambulatory, given orally
Eads (252)	AlOH, milk and cream by drip; hospitalized	40	1.5	All relieved but two
Steigmann (169)	Hospitalized 7–10 days; AlOH, milk and cream by drip	12	1–2	Large gastric ulcers only, 2.5 cm. +

Table 136 (Continued)

Author	*Treatment*	*Number Cases*	*Average Duration Pain in Days*	*Remarks*
Tidmarsh (103)	Half hospitalized; Mag. trisilicate	26	4–8	Bland diet; milk and cream every two hours, in 89 per cent of cases
Fogelson (30, 31)	Hospitalized and ambulatory; gastric mucin	12	3.0	In all cases
Atkinson (107)	Hospitalized and ambulatory; gastric mucin	43	1.7	In all cases
Brown (111)	Hospitalized and ambulatory; gastric mucin	37	8.0	In 97 per cent cases, "intractable ulcers"
Bernstein (142, 143)	0.2 mg. histamine phos. daily; bland diet with milk and frequent feedings; patients probably ambulatory	92	4.0	67 per cent free of pain after four injections

* All patients on Sippy treatment were relieved in 15 days and only 51 per cent on beef broth in place of powders were relieved in 15 days. For 46 patients on strict Sippy management in the hospital, the pain disappeared on the first to fourth days.

extract in relieving the distress of peptic ulcer. They do not show whether the "free acidity" must be neutralized or whether the maintenance of a pH of 2.0 or higher for one half the 24 hour period is adequate for the relief of distress. In fact, the studies of Kirsner and Palmer (38) and of Wosika and Emery (36) show clearly that the free acidity is controlled completely in only a small percentage of patients during the daytime and in none during the night (Table 137).

Dick and Eisele (12), using only frequent feedings of milk and cream, observed a disappearance of pain in less than one week, though one patient out of 31 had to have alkalis. The "rest cure" regimen gave early relief from pain. The frequent feeding of protein hydrolysate instead of powders or instead of milk and cream and powders is reported to provide early relief. The use of aluminum hydroxide and gastric mucin, which admittedly do not neutralize all the "free acidity" or raise the pH higher than 3.5, give relief from distress as early as the strict Sippy regimen.

In the only study comparing a "modified Sippy" management (the Sippy diet with powders six times daily) with aluminum hydroxide management (4 cc. hourly with Sippy diet), relief of pain occurred within two days on both managements except in cases of severe distress (167).

Comment. It would appear to be proven that strict neutralization is not requisite for early relief from distress. In addition, the evidence shows that

a schedule of frequent feedings with or without an antacid with or without hospitalization will provide relief from distress within two or three days in at least 85 per cent of patients with peptic ulcer.

The remaining patients, especially those with severe distress or a penetrating ulcer, require bed-rest and careful attention to the maintenance of

Table 137

SHOWING THE RELATIVE EFFECTIVENESS OF MILK AND CREAM AND THE VARIOUS STAGES OF THE SIPPY TREATMENT*

Groups	*Free Gastric Acidity in C.U. or M. eq.*	*Per Cent of Cases*			
		Milk and Cream Alone	*First Day Sippy*	*Second Day Sippy*	*Fourth Week Sippy*
I	No reading with free acid	7	10	14	7.1
II	No reading with free acid over 10	10	13	7	7.1
III	No reading of free acid over 20	16.6	13	35.7	28.5
IV	One or more readings over 20	66.6	63	42.8	57.0

* Wosika and Emery (36).

a complete or partial (pH 2.0 or 3.0) neutralization program. In some cases, belladonna and a sedative appear to be of definite benefit.

A well designed study to determine whether relief from distress occurs more rapidly on hospitalization than on ambulation when the same treatment is used has not been conducted.

TIME OF DISAPPEARANCE OF CRATER

Though, except for gastroscopy, the time of disappearance of the crater is the most reliable criterion available for estimating healing, relatively few articles on the medical treatment of peptic ulcer provide such observations.

It is interesting to point out how well the data from diverse sources agree on the rate of healing or filling in of a crater. In the dog, small acute ulcers which do not penetrate to the serosa heal at a rate of 1 to 2 mm. per day, while large ulcers (6 cm. in diameter) heal at a rate of 0.32 to 0.64 mm. per day (p. 149). In man, the chronic gastric ulcer is sometimes as deep or deeper than it is wide (Table 138), and the depth of the crater must be filled before its width can finally be epithelialized. Using hospitalization and a strict Sippy regimen, we (168) observed that ulcers averaging 4.0, 7.0, and 15.0 mm. in diameter healed at an average rate of 0.1, 0.2, and 0.5 mm. per day, respectively. Steigmann (169) treated a group of

large gastric ulcers by giving them a portion of a soft, bland diet every hours during the day and a continuous intragastric drip of from 2 2.5 l. of 1 per cent $Al(OH)_3$ during the day and night. This treatmen continued for seven or 10 days, after which the drip was discontinue 8 cc. of 4 per cent $Al(OH)_3$ was given every two hours with a bland The average rate of decrease in the depth and width of the ulcers was and 0.57 mm. per day, respectively (Table 138). It is striking how we

Table 138

RATE OF FILLING-IN OF "CRATER" OF LARGE GASTRIC ULCERS*†

No. Ulcer Patients	*Size of Crater Before*		*Size of Crater After*		*Days Observed*	*Mm. Dec. per Da*	
	Depth mm.	*Width* mm.	*Depth* mm.	*Width* mm.		*Depth*	
6	11	21	0	0	18	0.6	
11	30	41	2	3	90	0.3	
9	18	35	2	4	134	0.1	
8	16	22	8	5	11	0.7	
10	18	27	5	8	20	0.65	
12	20	22	3	10	32	0.53	
4	28	50	9	10	39	0.5	
7	30	18	8	10	61	0.36	
3	16	18	10	12	13	0.5	
2	32	20	10	18	14	1.0	
1	18	26	5	15	75	0.17	
5	13	25	3	18	30	0.3	
Average	21	27	5.4	9.4	44.7	0.48	

* Treatment was $Al(OH)_3$ milk and cream drip for 7–10 days in hospital a bland diet with $Al(OH)_3$ between meals.

† Steigmann (169).

data from these three sources check. In addition, the data from t groups of human patients show that the rate of healing was approx the same with the use of alkaline powders and of aluminum hyd the patients being hospitalized in both instances.

All the evidence on the rate of filling of an ulcer crater we hav able to find is summarized in Table 139. In all studies, except o patients were hospitalized and given either duodenal feeding, or f feedings, or a strict Sippy regimen, or protein hydrolysate. In exception, only a part of the patients were hospitalized and a soft diet with $Al(OH)_3$ was given four times daily.

Table 139

RATE OF FILLING-IN OF THE ULCER CRATER WITH VARIOUS TREATMENTS

Author	Treatment	Number Cases	Time of "Healing"					
			Gastric Ulcer			Duodenal Ulcer		
			Number Cases	Average Days	Range Days	Number Cases	Average Days	Range Days
. (254)	Hospitalization; duodenal feeding	5	5	35	..	..	..	..
n (255)	Hospitalization; duodenal feeding	15	15	28	..	..	..	..
(256)	6 weeks in hospital; milk, cream, eggs, fish, Vichy water	33	33	40	14–100	..	..	..
ns et al. (168)	Hospitalization; strict Sippy plus belladonna and sedative	69	6	42	18–68	62 (63)	37 (40)	18–68 18–230
et al. (42)	Hospitalization; frequent feedings of protein hydrolysate plus Dextrimaltose	12*	8	16	10–30	4	15	10–25
ton (253)	Hospitalization; Sippy with atropine and aspiration	36	..	..	..	36	45	7–140
(43)	Hospitalization; protein hydrolysate with Dextrimaltose	13†	3	21	..	6	21	..
250)	Ambulatory and hospitalization; soft diet and Al-OH 4× daily	13	5‡	33	21–41	8§	28	7–56
Eisele (12)	Hospitalization; milk and cream, frequent feedings	..	..	..	..	25‖	46	15–78

dan and Bowman (257) followed 41 patients with gastric ulcer on the Sippy regimen. Nine did not heal 3 "healed" within three or four weeks; 19 "healed" within seven to 14 weeks, the x-ray examination made rather far apart in the latter cases. Ricketts, Palmer, Kirsner, and Hamann (170) report that they d complete disappearance of the crater in only 60 per cent of 114 gastric ulcers.

Liver extract parenterally 2× weekly.

No x-ray examination in two patients and crater still present at 21 days in two others.

One gastric ulcer not healed at 49 days.

One duodenal ulcer not healed at 60 days.

Crater had disappeared within 75 days in 93 per cent of 41 patients. In two, the crater persisted to s.

study of the data in the table will show that with various therapies rater of a duodenal or gastric ulcer will usually disappear within 60 provided a regimen of frequent feedings of a semiliquid or soft, bland with some antacid or a diet of high buffering capacity is followed. It o clear that some craters disappear very slowly under the strictest ens. For example, Ricketts, Palmer, Kirsner, and Hamann (170)

have reported that they obtained complete disappearance of in only 60 per cent of 114 cases of gastric ulcer.

Moreover, there is no evidence showing that the strict *Ulcer* continuous *ambulatory drip*, is *superior to* the *rigid regimen* given *hospitalization or ambulation* in so far as the rate of filling in of the is concerned. To establish that a difference does exist, evid experiments of the type cited under the previous topic of "Disa pearance of symptoms" must be presented. Nevertheless, as evidence to the contrary, *we strongly recommend that patients with ulcer be hospitalized and given a strict management using antacid or ambulatory drip.*

Even though there is no quantitative evidence showing th increases the rate of disappearance of symptoms and of the cr internists of experience knows that many patients who fail to re under ambulatory treatment will do so when the treatment is continued with the patient at rest in bed.

Comment. The paucity of the results of post-treatment graphic examination in articles in the literature is striking. T pearance of the crater is the best criterion of the success of a m it would appear that a definite routine of post-therapeutic graphic examination should be employed. For example, the fir tion should be made two or three weeks after the start of tre them at one, two, or three week intervals, depending on the a pearance of the crater and the amount of x-rays to which the been exposed. Such an x-ray follow-up is definitely required with a gastric ulcer to decrease the chances that a malignant u treated medically, and theoretically it should be a part of a medical and some surgical managements of patients with pep

Miscellaneous Factors Affecting Healing or Res to Therapy

Age. This has been reported to be a factor affecting the pat Though an ulcer in a young person probably heals faster than this has not been established by the evidence submitted [17].

Duration of Symptoms and Frequency of Recurrences. been thought to increase the difficulty of the management exacerbation or recurrence of the disease. When strict medi ment is used with hospitalization and antacids, the immediate good, regardless of the number of recurrences [171–173]. Ho strict management with bed-rest and antacids is not used, appear to be the case [2, 164]. More evidence on this point

or Ulcer. It is generally conceded that anastomotic ulcer is more to manage medically than gastric or duodenal ulcer. There are, , no data available to substantiate this clinical impression.

currences of Peptic Ulcer after Medical Treatment

Incidence of Recurrences

rvations of patients having peptic ulcer during the past 50 years rate that one should not speak unequivocally of the cure of the As indicated elsewhere, some patients will go as long as 20 years a recurrence and others will develop a recurrence within six after the ulcer is healed. Since the treatment of the acute exacerbae disease is so readily managed in most cases, the chief therapeutic today is to ascertain how best to prevent recurrences.

e literature prior to 1913, when the diagnosis of ulcer was not as it is today, the incidence of recurrences varies from 27 to 87 per periods of follow-up ranging from 0.5 to 1.5 years up to 10 years. to a large extent are unreliable (61). "Permanent cures" ranging to 60 per cent for varying periods up to five years were reported general use of roentgenographic examination (164, 175–177). an and Balfour (61) in 1935 wrote that "apparently, under circumstances and adequately sustained treatment, there is a y of a five year cure for duodenal ulcer in 50 per cent of cases." more definitive data to be found in the literature are summarized 140. It will be noted that the incidence of recurrences during the ranges from 9 to 92 per cent. The smallest percentage occurs use of the Sippy regimen, in which a strict management continues from nine to 12 months. When practically no management was ong with parenteral injections of inert substances, the recurrence 92 per cent. With six feedings and alkalis as indicated to relieve the recurrence rate during the first year ranges from 50 to 80 per

average of the data for each time period shown in Table 140 is in Fig. 132. The data of Emery and Monroe are omitted because ude failures as well as recurrences and would weight the average ly, since it would represent one half of the patients if included. It e noted that the curve plateaus after the fourth year, which is a r than that observed by Nielsen.

gth of Average Symptom-free Period after Therapy

d of expressing the pre- and post-therapeutic course of a patient of patients in regard to the number of recurrences in time, the

Table 140

INCIDENCE OF RECURRENCES AFTER VARIOUS MEDICAL TREATMENTS OF PEPTIC ULCER

Author	Type of Patient	Type of Treatment	Period of Observation in Years*												Type of Ulcer
			0.5 yr.		1 yr.		2 yrs.		3 yrs.		4 yrs.		5 yrs.		
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Crohn (258)	Ward	Bed-rest; modified Sippy	86	8	86	31	58	43	32	70	18	67	..	..	Gastric and duodenal
Jordan & Kiefer (182)	Private	Bed-rest; complete Sippy	..	..	392	9	268	19	172	30	84	39	37	44	Duodenal
Lucas & Monroe (180)	Clinic	Chiefly five meals and alkaline powders			1085	79		24		23		24		26	1926 patients; average duration 3.9 years; gastric and duodenal
St. John & Flood (179)	Ward	Bed-rest 18 days; modified Sippy	..	..	..	.	140	65	90	60	79	69	59	78	Duodenal
Holland & Logan (259)	Private	Chiefly ambulatory; frequent feeding and alkalies	..	..	..	.	..	..	..	..	..	..	312	64	Duodenal
Murray et al. (181)	Ward	Bed-rest; milk and cream; alkalies only as required for pain	..	..	..	.	..	..	230	44	..	..	63	48	Gastric
									152	36					Duodenal
Raimondi & Gollen (260)	Contract	Six feedings plus Al(OH)$_3$; some hospitalization	111	30	151	64	99	83	..	..	..	..	..	..	Gastric and duodenal
Flood (178)	Ward	Bed-rest 18 days; modified Sippy	..	..	281	40	215	63	191	68	155	75	137	78	233 Duodenal
Sandweiss et al. (261)	Clinic	Parenteral injections	..	..	94	92	..	..	..	..	..	..	..	..	Duodenal chiefly
		Diet and alkalies with and without hospitalization	..	..	139	50	..	..	..	..	..	..	..	..	
Ivy et al. (145)	Clinic	Intestinal extract injections			46	68	33	66	..	..	..	..	..	..	Chiefly duodenal
Shelson (164)	Clinic	Hospitalization; frequent feeding; alkalies as necessary			181	71	136	87	93	90	69	94	44	92	Gastric and duodenal
			197	2	2872	64	791	80	1	1	42	1	1	2	

of the average symptom-free period may be used. Flood (178) the clinical course of the patient by grading "complete freedom of ms as 4, mild gas and belching as 3, typical symptoms not inter- work as 2, and symptoms interrupting work as 1." Symptoms 4 and 3 are called "satisfactory." He has reported on 233 patients tal period of 1603 patient years. Sixty-three per cent (1006) of the were "satisfactory"; 24.3 per cent (390 years) were grade 2 or ately severe; 12.7 per cent (207 years) were grade 1, or incapaci- Seven hundred fifty-six recurrences occurred in 1603 years or at a

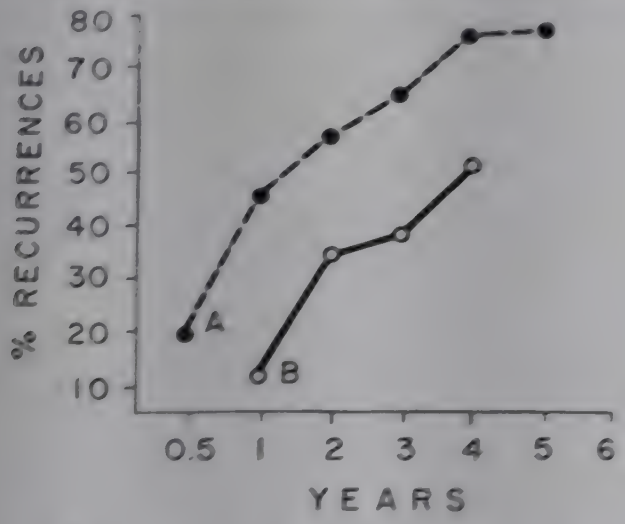


FIG. 132. (A) Showing curve of incidence of recurrences as obtained from data in Table 140.

(B) Showing curve of recurrences if patients who are improved though having had a recurrence are subtracted. For example, 90 per cent of patients at one year are symptom-free or improved. This places medical therapy in a more favorable light.

one to every 2.1 years. In 225 patients observed by St. John and (179), the average "satisfactory" period during an average of 3.3 was 69 per cent, or the average patient was "satisfactory" 69 per the time. We (145) studied a group of 46 patients who had an e symptom-free period of 0.3 ± 0.3 years before treatment and of 0.7 years after treatment.

FACTORS AFFECTING RATE OF RECURRENCES

PE OF TREATMENT OF ACUTE EXACERBATIONS. *Treatment vs. No ent.* The only data rendering a comparison of the long-term results treatment" with those of a "treatment" have been provided by

Emery and Monroe (180). Their data (Table 141) show that 81 per c
of the treated cases were much improved "whereas only 48 per cent of
untreated cases were much improved over an average period of 3.9 yea
Similar evidence over a period of one year of observation is presented

Table 141

FOLLOW-UP RESULTS OF NO MANAGEMENT COMPARED WITH MEDICAL MANAGEMENT* †

	Medical Treatment		*Without Treat*	
	No.	*Per Cent*	*No.*	*Per*
A. Without symptoms	149	13.7	30	2
B. With very few symptoms	397	36.5	11	3
C. Definite improvement	335	30.8	20	1
D. Improvement	69	6.3	5	
E. No improvement	135	12.5	60	4
A + B	546	50.2	41	3
C + D + E	539	49.6	85	6
A + B + C	881	81.0	61	4
D + E	204	18.8	65	5

* Emery and Monroe (180).

† Average duration of observation after treatment presumably 3.9 years.

Sandweiss et al. (Table 140). They found a recurrence rate of 92 per
in a group of patients which received only parenteral injections of
specific substances as compared to a recurrence rate of 50 per ce
another group which received a diet with alkalis. It is clear fro
evidence that *recurrences occur more frequently when no special therapy is g*

Strict vs. Less Strict Regimen. The lowest rate of recurrences sho
Table 140 is that reported by Jordan and Kiefer, who used a "
Sippy" regimen. Emery and Monroe (Table 142) obtained some
better results even than Jordan and Kiefer with a "strict Sippy." In
tion, their results with a "strict Sippy" are significantly superio
"partial Sippy" regimen or a schedule of five meals plus alkalis
142). The results of Flood (Table 143), although they extend only
period of one year, also show that *fewer recurrences occur on a "strict diet"
on a "moderately strict" or "broken diet."*

The beneficial effect of a complete Sippy or a strict dietary regi
reducing the incidence of recurrences is not necessarily due to su
healing of the ulcer. It is more likely due, in our opinion, to the for
of careful eating and living habits, which tend to prevent recurre

Table 142

FOLLOW-UP RESULTS OF MEDICAL MANAGEMENT IN 1085 PATIENTS*†

Treatment	Number of Cases	Per Cent without Symptoms A	Per Cent with Few Symptoms B	A + B	Per Cent Definitely Better C	Per Cent Much Better D	Per Cent Not Better; Complete Failures E
mplete Sippy	58	25.0‡	31.0	56.0	34.4	5.1	5.1
tial Sippy...	89	13.4‡	38.2	51.6	33.5	6.7	7.8
e Meals Plus alies	938	13.1	36.7	49.8	30.3	6.4	13.3

Emery and Monroe (180).
Average duration of observation after treatment 3.9 yr.
The χ^2 on the difference between 25.0 per cent and 13.4 per cent is 3.6, a statis- significant difference.
.8 per cent of entire group was free of symptoms for 3.9 years.
"Complete neutralization" for nine to twelve months.
"Complete neutralization" for four to five months, or incomplete neutralization rious reasons.
Smooth, bland diet with various amounts of alkalies.
te: If patients with no symptoms and few symptoms (A + B) are added, there ignificant difference in the results of the three managements.

Table 143

RELATION OF INCIDENCE OF RECURRENCES TO PATIENT'S ADHERENCE TO DIET*†

Diet	No. Cases	Per Cent without Symptoms	Per Cent with Moderate Symptoms	Per Cent with Severe Symptoms
diet	44	43 (19)	39 (17)	18 (8)
rately strict diet	53	43 (23)	41 (22)	15 (8)
n diet	76	62 (47)	30 (23)	8 (6)

Flood (178).
All patients observed one year.
te: None of the differences is statistically significant, except those "without oms" on a strict (43 per cent) and on a "broken diet" (62 per cent), and on a erately strict" (43 per cent) and a "broken diet" (62 per cent).

Hospital vs. Ambulatory Management. There are no good data showing effect of hospital vs. ambulatory management on the incidence of re rences. A study of the data in Table 140 would suggest that hospitaliza tends to decrease the incidence of recurrences. However, other factors have been involved in causing the differences noted. The results o experiment in which ulcer patients are given the same therapy excep hospitalization and ambulation are required. The patients for each g will have to be selected so as to have the two groups approximately e as regards the severity of the disease. The importance of this is show the results of Flood (178) who obtained 80 per cent of "satisfactory" re in ambulatory patients and only 63 per cent in hospitalized pat because the more severe cases were hospitalized.

Variation in Tendency to Recurrences in Groups of Patien is well known that ulcer disease in some patients resists medical ma ment more than in other patients. Some investigators select what term to be a group of "intractable ulcer patients" for testing new t peutic procedures.

The "medical intractability" of an ulcer patient to treatment exacerbation or of recurrences is said to be an indication for surgery there is no doubt that many of the patients who are susceptible to rences are finally referred to the surgeon.

That such a difference actually exists as regards recurrences in cally managed groups is demonstrated by certain items of data in T 140 and 141. For example, 23.8 per cent of the patients of Emer Monroe (Table 141) who received no treatment remained sympto for an average period of 3.9 years, whereas only 8 per cent of Sand patients who received no treatment (i.e. parenteral injections) (Tab remained symptom-free for one year.

This fact must be taken into consideration in the interpretation results of therapy.

Factors Prognostic of Recurrences

Is It Significant That the Ulcer Be Healed at Conclusi Hospital Treatment? As indicated elsewhere, it has been as theoretically that the answer to this question should be "yes." He evidence presented by Natvig et al. (181) shows that this may not b Their treatment required four to six weeks of bed-rest with fr feedings of milk and cream for from four to six weeks, with alka warm compresses as indicated for pain. After this period, the patie released from the hospital. In 127 cases of gastric ulcer, the cra disappeared in 60 per cent. In 217 cases of duodenal ulcer, the cra disappeared in 80 per cent. In the case of gastric ulcer, 40 per ce

6 per cent without a crater on release remained free of symptoms for years. In the case of duodenal ulcer, 22.5 per cent with and 36 per without a crater on release remained free of symptoms for three years. e differences are not significant; hence, it would appear that the plete healing of an ulcer on the cessation of from four to six weeks of management is not decisively important for the prevention of rences. Or, it might be said that the rate of healing of an ulcer is ignificantly prognostic of a tendency to recurrences. More evidence is point is needed.

ELATION OF SIZE OF ULCER TO INCIDENCE OF RECURRENCES. In a of 135 patients, Natvig et al. (181) found that a patient with a c ulcer less than 1 cm. in width is twice as likely to have a recurrence ree years as a patient with an ulcer larger than 1 cm. in diameter.

ELATION OF BULBAR DEFORMITY TO INCIDENCE OF RECURRENCES. In a of 228 patients with duodenal deformity, no correlation was found een the degree of deformity and the prospect of a recurrence (181). ever, Jordan and Kiefer (182) found that response of the duodenal mity to treatment has some significance in prognosticating a recur- . A recurrence occurred during a period of five years observation in r cent of patients who showed no improvement and in only 10 per who showed improvement of duodenal deformity in response to cal management.

ELATION OF SITE OF ULCER TO RECURRENCES. No significant difference e tendency of a gastric and duodenal ulcer to recur has been found le 140) (120, 183).

omment. Anatomic factors do not appear to be important in deter- g recurrences. The factor of improvement of the duodenal deformity sponse to therapy is a clinical rather than an anatomic factor.

ELATION OF DURATION OF DISEASE TO INCIDENCE OF RECURRENCES. al observers have presented evidence (164, 181, 184) indicating that onger the patient has had ulcer symptoms, the more likely the patient have a recurrence after therapy (Table 144).

his teaches that the patient would do better to consult the physician in the course of the disease and submit to a strict management (164, 184).

ELATION OF PREVIOUS HISTORY OF REMISSION TO RECURRENCES. Ac- ng to data submitted by Emery and Monroe (180), the length of the om-free period prior to therapy checks well with the length of the om-free period after therapy. Of the 500 patients recorded in Table 1 per cent gave a history of remissions lasting less than one year, checks well with 79 per cent of patients who had recurrences within ear after therapy.

Table 144

RELATION OF DURATION OF ULCER SYMPTOMS TO RECURRENCES AFTER THERAPY (181)

Site of Ulcer	Duration of Symptoms					
	Less than 5 Years			More than 5 Years		
	No. of Cases	Symptom-free*		No. of Cases	Symptom-fr	
		No. of Cases	Per Cent		No. of Cases	Per Ce
Stomach	94	52	55	58	14	2
Duodenum	134	55	41	96	24	2
Total	228	107	47	154	39	2

* Symptom-free three years after therapy.

The difference between 45 per cent and 25 per cent is significa ($\chi^2 = 15.9$).

Table 145

LENGTH OF REMISSIONS AS REVEALED BY HISTORY IN 500 PATIENTS

Remissions lasting from a few weeks to a few months	3
Remissions lasting for two years	
Remissions lasting for three years	
Remissions lasting from three to six years	
Remissions lasting from six to nine years	
Remissions lasting for 20 years	

* Emery and Monroe (180).

† In 500 patients relief occurred in 131 (26 per cent) spontaneo in 5 or taking a vacation, and in 364 (73 per cent) on taking ma management.

‡ This number yields a figure of 71 per cent for the incidenc recurrences within one year, which checks with 70 per cent of patients (Table 141) who were not completely relieved of sympt during the first year of therapy.

RELATION OF RESISTANCE TO THERAPY CONSISTING OF BLAND STRICT DIET TO RECURRENCES. St. John and Flood (179) have good evidence to show that the prognosis is bad in regard to r if the patient resists therapy or is not relieved of symptoms w weeks in the hospital on strict management or is relieved acc

...corrence while in the hospital. In 220 patients followed for 842 ...rs (average 3.3 years), the average "satisfactory" period was 503 ...is, the patients were symptom-free 60 per cent of the time. In 57 ...to related treatment but were relieved before release and who ...wed for 193 years (average 3.5 years), the average "satisfactory" ...57 years, or 30 per cent of the time. Flood (178) found that 50 ...to resisted therapy but were relieved before release from the ...od who were followed for an average of six years were "satis- ...4 per cent of the time, in contrast to 60 patients who responded ...were "satisfactory" 70 per cent of the time during an average ...13.7 years. In 30 patients subsequently subjected to operation, ...r "satisfactory" period was 43 per cent over an average period of

...RANCE TO ALKALI THERAPY. Jordan and Kiefer (182) found ...r cent of 47 duodenal ulcer patients who developed recurrences ...ceptible" to the development of alkalosis as compared to only ...of those who did not develop recurrences. The recurrences were ...to the inability of these patients to tolerate enough alkali to ...ir symptoms and to promote healing of the ulcer. The presence ...sion (systolic above 150 and diastolic above 90 mm. Hg) and ...rphritis appeared to predispose to a low tolerance to alkalis and ...s. These observations require further study.

...ON OF OBSTRUCTION TO RECURRENCES. In some patients, as ...n, indicated by retention of as much as 50 per cent of a barium ...ix hours, will entirely disappear on medical management. In ...obstruction will decrease after two to eight weeks but will not ...entirely; this indicates a cicatrical type of obstruction.

...(176) found that there was no greater tendency toward recur- ...ations with than in those without the complication of a *gastric* ... The same held for patients with a *moderate* obstruction which was ... The patients with the *more severe grade of persistent* obstruction were ...early and without following them for a prolonged period. ...d Kiefer (182) agree with the foregoing observations but observe ...rence is three times more frequent in patients with persistent ...six hours at three weeks). This is in agreement with the general ...pression and teaching of ourselves and others, but more evi- ...n that which is available is required to establish it as a fact. ...ence is usually indicates retention, would be a symptom indi- ...**lihood of a recurrence** (182).

...ON OF SEVERITY OF PAIN TO RECURRENCES. Jordan and Kiefer ...d no difference in the severity of pain and its radiation between ...hich the ulcer did and did not recur. However, they found

nocturnal distress and epigastric tenderness to be twice as comm
those patients who suffered recurrences.

Relation of Occult Blood to Recurrences. The occurre
occult blood on admission and its persistence for more than one w
bed-rest and a strict Sippy regimen was four times more frequ
patients with recurrences (182).

Relation of Acidity and "Resistance to Neutralizatio
Recurrences. The acidity of the gastric contents in response to a te
has been found not to be significantly prognostic of recurrences (18
183) in medically managed patients. But as Emery and Monroe
point out, the quantity of acid secreted is not indicated by test
acidity. Jordan and Kiefer (182) took this into consideration wh
determined the "resistance to neutralization." This was done by ti
the unneutralized acid one half hour after the last powder. Though
cent of the recurrent cases and only 24 per cent of the nonrecurre
showed a persistently high acid (over 50 C.U.), the difference
statistically significant.

These tests do not consider the extent to which excessive n
secretion is involved in recurrences. Though it is known to be exc
most patients with duodenal ulcer, its relation to recurrences
been carefully studied. Since the effect of vagotomy on nocturna
tion is now being studied clinically, the answer to this question
forthcoming.

Relation of Age and Sex to Recurrences. Age has been rep
have no significant relation to prognosticating recurrences (170, 18
However, others have presented evidence indicating that when th
occurs in persons above the age of 40 years, the likelihood of recur
increased (171, 172). There is no evidence that sex is a factor pred
to recurrences. Both these factors require further study.

Summary. Features of the *history and physical* examination which
to prognosticate a tendency to recurrences of ulcer disease are as
(a) a long history of ulcer disease, (b) an average length of remi
less than 0.6 of a year, (c) more than one hemorrhage, (d) n
distress, (e) epigastric tenderness.

The following features of the *response to therapy* appear to be c
in indicating a tendency to recurrences: (a) absence of relief wi
weeks of bed-rest and strict management, or the recurrence o
while in the hospital; (b) intolerance to alkalis; (c) persistent ob
or a six hour retention for longer than three weeks; (d) persi
occult blood for longer than a week; (e) degree of improv
duodenal deformity, but not the degree of deformity *per se*.

Other *prognostic features* are: (a) Resistance to neutralization of gastric ntents and the amount of nocturnal secretion would seem to be impor- it, though they have not been established by good evidence; (b) An age onset of more than 40 years may predispose to recurrence, but sex does t appear to do so.

More evidence is needed to establish firmly those features of peptic cer disease which predispose to recurrences.

Apparent Inciting Causes of Recurrences

The apparent inciting causes of peptic ulcer have been discussed else- here (Chapter 20). Those which have been suspected of exciting recur- nces are shown in Table 146. It should be noted that the two more recent

Table 146

Apparent Inciting Causes of Peptic Ulcer Recurrences

Author	*Number of Patients*	*Fatigue, Per Cent*	*Emotions, Per Cent*	*Infections, Per Cent*	*Diet, Per Cent*	*Miscellaneous, Per Cent*
nhorn, 1930 (262)	800	..	7	56	9	28
nery & Monroe, 1935 (180)	1,279	42	32	21	5	..
wies & Wilson, 1937 (263)	52	21	35	25	..	19
nkelson, 1938 (264)	350	..	24	15	30	31
od, 1948 (178)	233	..	40	10	25	25
iedenwald, 1932 (265)	200	..	..	42	..	58

ticles indicate that infections are less concerned than did earlier articles aling with this subject. Many authors or patients also implicate smoking d the drinking of alcoholic and caffeinated beverages. The most parent fact is that no factor among those suspected is particularly out- anding, especially in view of the widely accepted opinion that a tension ate is the principal excitatory cause of both the initial attack and the currences. The skeptic could maintain that the factors listed only present guesses and that when the gun is loaded either a tension state, ysical fatigue, lack of sleep, dietary indiscretion, an upper respiratory fection, or a focus of infection, etc., may pull the trigger.

Prevention of Recurrences

The willingness of the patient to cooperate by continuing on a strict gimen of diet and on a prescribed schedule of rest and vacation are, we

believe, the most important factors in the prevention of recurrences. Ma authors point out that carelessness in regard to these factors accounts f most recurrences. Nevertheless, it is not possible by the available eviden to establish unequivocally the foregoing contention. And it is not easy assemble reliable evidence to determine which of the two factors is mo important, or whether other factors than diet, rest, and calm are impo tant. Perhaps, as some have stated, the adherence to a strict diet regimen alone is not certain to help unless the patient is able to live a "ca life." If we possessed unequivocal data on these points, we would be in stronger logical position to convince the ulcer patient that the permanen of his "cure" is in his own hands—a fact which will obtain until some w is discovered for preventing recurrences by a management which requi little or no cooperation from the patient.

It would appear that to discover and eradicate "foci of infection" obviously important, if for no other reason than for the good of the gen health of the patient. (See the role of infection in ulcer following s burns, p. 288.) Since smoking, alcohol, and caffeine are suspects, t should be eliminated if for no other reason than a "safety first hypothes they are obviously unhygienic. The same should apply to all foods wh appear to cause distress. The importance of a soft, bland diet and of ke ing a little food in the stomach most of the 24 hour day for the life of t patient would seem to follow from all experimental studies on the fac concerned in maintaining the chronicity of an ulcer. The significanc brief periods of rest or relaxation during the day, regular habits of sl and short vacations at regular intervals would favor smooth physiol operation of the digestive organs and all bodily systems.

Prevention of Recurrences with an Enterogastrone-containing Extract

We have presented elsewhere (Chap. 13) the evidence showing th substance which prevents the development and establishes some resist against the recurrence of ulcer in experimental animals exists in ap priately prepared extracts of the upper intestinal mucosa. An experi has been undertaken to determine whether this "anti-ulcer" substan active in man and the results will be briefly outlined.

A group of 46 patients was selected on the basis of the presence history of peptic ulcer of at least four years duration with frequent re rences. The average duration of the disease in these patients was 15 y and the average longest symptom-free period during the two years to treatment was 0.3 ± S.D. 0.3 years. Each patient was subjected t upper gastrointestinal roentgenographic study at the beginning of t ment and at monthly or bimonthly intervals for the first six mo

her examination was made at the end of the treatment period, and
ys if a patient complained of symptoms.

The past history of the patients was used as the control in this study.
was based on the assumption that a patient who shows periods of
ess every week or month while on ambulatory management or a
ern of frequent recurrences over a period of four years or longer is
ely to undergo a spontaneous marked decrease in recurrences.

n order to make a valid appraisal of the results, as few changes as
ible were introduced into the therapeutic program which the patient
following at the time the patient consulted us. When necessary, strict
agement was employed with six feedings of a soft, bland diet with
inum hydroxide or phosphate gel. In such instances, usually when
ulcer was penetrating in type, this therapy was continued until the
er disappeared. Only two of the 46 patients were hospitalized for a
trating ulcer.

The enterogastrone-containing preparation was given intramuscularly
patients for 12 months, four patients for nine months, and six patients
ive to seven months. Nine of the patients were injected three, and the
ainder six, times a week. Any return of symptoms has been called a
rrence. In those patients referred to as improved, the recurrences were
uestionably less frequent and severe, the distress in some cases lasting
one or two days and subsiding spontaneously; in others, it was doubt-
whether the symptoms were due to an active ulcer.

The results up to July 1948 are shown in Table 147. Recurrences have
occurred in some patients for from 12 to 58 months. They have
rred three to 23 months after the cessation of therapy in seven patients
were free of symptoms during the treatment period of nine to 12
ths. The most accurate way, perhaps, to express the benefit of the
apy is to point out that the average longest symptom-free period during
ears prior to therapy was 0.3 ± S.D. 0.3 years, and after therapy
been 0.9 ± S.D. 0.7 years. The difference noted could occur by chance
than once in 100 such experiments.

We have interpreted these results as showing that the "anti-ulcer"
tance which was shown to be active in the dog is also active in man.
ould be made clear that we have no evidence showing that the injec-
of enterogastrone-containing preparations is superior to other forms
edical management of the acute exacerbations of peptic ulcer, and
there is no evidence to show that the present enterogastrone-contain-
preparation is superior to ordinary medical management for the
rity of patients with peptic ulcer, particularly in view of the incon-
ence, the cost of the product, and the imperfect results. However, we
ve its trial on an experimental basis is indicated in those patients who

do not have a significant degree of pyloric stenosis, who frequently ha periods of severe distress while working and attempting to follow adequ dietary and antacid management, and who defer or refuse operat intervention.

Table 147

STATUS OF 46 PATIENTS WITH A LONG HISTORY* OF PEPTIC ULCER TREATED FOR FIVE TO 12 MONTHS WITH AN ENTEROGASTRONE-CONTAINING PREPARATION

Months after Start of Therapy		12	13–18	19–24	25–30	31–36	37–42	43–48	49–54	55
No. Cases		46	40	35	29	21	9	6	4	
		Status at Six Month Intervals								
Symptom-free	*No.*	19	20	14	11	8	5	5	4	
	Per Cent	41	50	40	38	38				
Improved†	*No.*	21	14	14	15	10	3	1		
	Per Cent	46	35	40	52	48				
Not Improved‡	*No.*	6	6	7	3	3	1			
	Per Cent	13	15	20	10	14				
Operated Upon		3§	1	1		1				

* The average longest symptom-free period during two years prior to the the was 0.3 ± 0.3 year.

† Definitely fewer recurrences, and in most instances milder.

‡ Recurrences of same frequency.

§ Two patients with high-grade organic pyloric obstruction who were advised operated on before the treatment was started.

Radiation Therapy of Peptic Ulcer

INTRODUCTION

Radiation therapy has been used in patients to produce a hyp anacidity with the idea of promoting the healing of an ulcer that ha responded well to medical management and of preventing recurrenc gastric and duodenal ulcer.

EXPERIMENTAL OBSERVATIONS ON ANIMALS

The exposure of the upper abdomen of the dog to an appropriate of x-rays usually causes a hypernormal secretion of gastric juice for

wo days, followed by a depression or abolition of the secretion of acid the stomach. When only the stomach is exposed, only depression of l secretion is observed (185–188). Moderate amounts of x-radiation duce edema, degenerative changes in the epithelial cells, leucocytic ltration, and hyperemia of the gastric mucosa: larger doses cause rosis and ulcer formation. It should be remembered that the intestines more sensitive than the stomach (189, 190). Permanent histologic nges occur in the gastric mucosa with a dose of x-rays which depresses secretion of acid, even in those cases in which the secretory response meal returns to normal in six weeks after exposure, which is the rule the Pavlov-pouch dog.

Observations on Man

Technic of Radiation. This topic will be considered first to serve as background for the subject matter to follow.

In order to deliver as little x-radiation as possible to tissues other than acid-secreting mucosa, two or three days before treatment the stomach visualized with a small barium meal and the contour of the fundus and pus are outlined on the skin of the abdomen and back. The anterior l posterior portals or the part to be exposed to x-rays are so placed that st of the x-rays are focused only on the fundus and corpus (Fig. 133).

The characteristics of the radiation used are a H.V.L. (half-value layer) h 1.5 mm. of copper produced by 200 P.K.V. (peak kilo voltage) and nm. of copper and 1 mm. aluminum filtration, the intensity of the liation being approximately 33 r in air per minute and obtained with milliamperes and a focal skin distance (F.S.D.) of 50 cm. The depth dose calculated by assuming that the gastric mucosa of the empty stomach s in a plane located two thirds of the distance from the skin of the back the anterior-posterior diameter of the body in the epigastric region.

The technics of irradiation which have been used are shown in Table 3.

Effect on Gastric Secretion. Bruegel, in 1917, used x-ray irradiation the stomach for the treatment of peptic ulcer in man (191). Since then merous reports have appeared in the literature regarding the effect of procedure on gastric secretion and the clinical course of peptic ulcer. good purpose would be served by reviewing this literature because the se of x-rays employed was too variable and the studies on gastric secre- n and the course of peptic ulcer were too meager (192).

In general, these reports show that a decrease in the secretion of acid ulted. However, irradiation of the pyloric portion of the stomach as d in the treatment of polycythemia has no significant effect on gastric retion (193, 194).

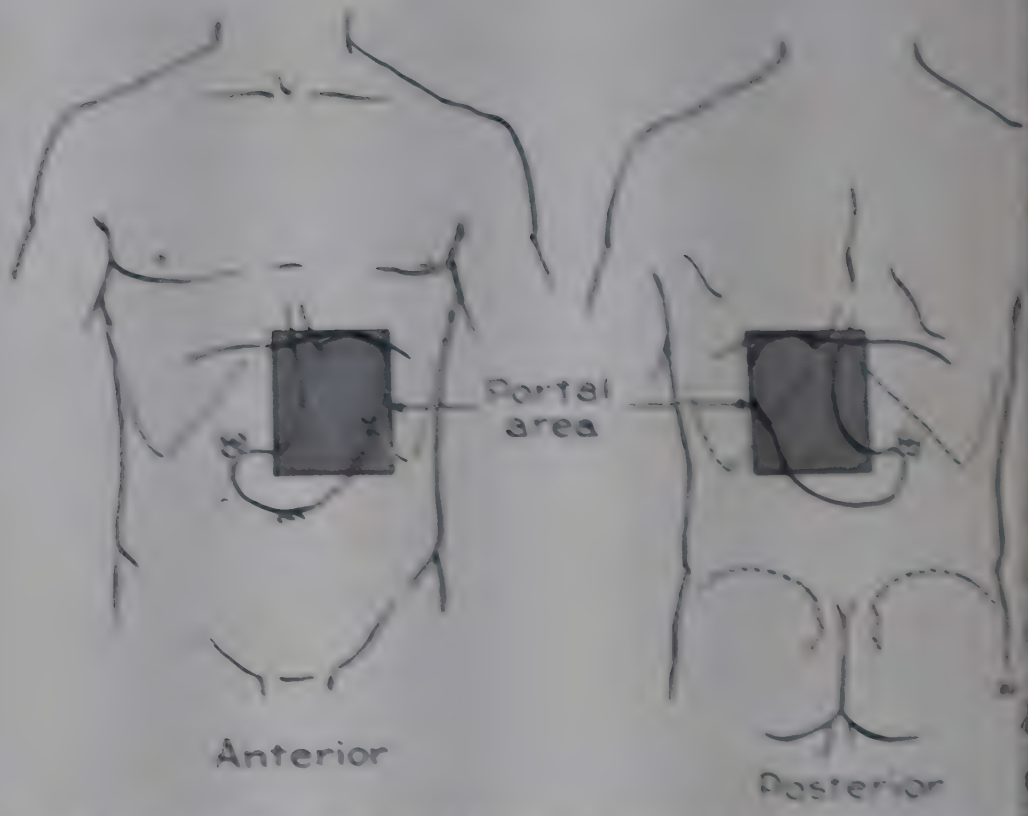


FIG. 133. Approximate portals used in anterior and posterior radia... fundus and corpus of the stomach. (Redrawn from Ricketts, Palmer, K... Hamann: *Gastroenterology*, **11**:791, 1948.)

Table 148

TECHNICS OF IRRADIATION*

Technic	No. Treatments per Portal	Duration of Radiation Days	Size of Portals Cm.	Total Dose
A	5 (or 6	12–14	15 × 15	2...
B†	5 (or 6	11–14	13 × 13	1...
C	5	11–12	13 × 13	1...
D	3	6– 7	13 × 13	1...

* Ricketts, Palmer, Kirsner, and Hamann (170).

† In A, C, and D technics, the dosage varied because a constant ... used without regard to size of portal and patient. Obese patients were ... portals the same day.

‡ The depth dose was fixed, the surface dose varying with the ... patient; otherwise, the surface dose was fixed.

Note: The dose given is the total dose.

...ent extensive investigations have been reported recently by ...Palmer, Kirsner, and Hamann (170). These results are summ... Table 149. The maximum depression of acid secretion is

Table 149

...SECRETORY RESPONSE TO 0.01 MG. OF HISTAMINE HYDROCHLORIDE PER ... KILO BODY WEIGHT AFTER EXPOSURE TO X-RADIATION[a]

...tion of ...)	Number of Cases	Per Cent	Amounts of Irradiation in "r"							
			A 1000–2500		B 1000		C 1100–1500		D 600–1000	
			No. Cases	Per Cent	No. Cases	Per Cent	No. Cases	Per Cent	No. Cases	Per Cent
Patients with Gastric Ulcer										
...e	32	68	10	91	11	92	11	69		
...ore than ...	10	21	1	9	0	0	9	56		
... per cent	5	11	0	0	1	8	4	25		
...	47	100	11	100	12	100	24	150		
Patients with Duodenal Ulcer										
...a ...	108	29	23	50	43	40	40	22	2	9
...ore than ...	109	32	15	33	37	34	53	31	3	14
... per ...	136	39	8	17	27	26	84	47	17	77
...	353	100	46	100	107	100	177	100	22	100

...ts, Palmer, Kirsner, and Hamann (170).

...per cent of cases) observed within a month. The anhydrhydria ... in 56 per cent of cases of gastric and 85 per cent of cases of ...lcer within six months and within one month in about roughly ... the cases. In two thirds of the cases which received over 1100 r, ... did not return to normal in the course of time.

...ON GASTRIC MUCOSA. The late effects of x-radiation on the ...cosa in animals consist of a combination of atrophy, proliferation, ...plasia, and fibrosis (195). In man, inflammatory changes in the ...ncident with the depression of acid secretion are seen gastro-

scopically and histologically. Months or years later, atrophy of the mu has been observed (196, 197).

Effect on Healing of Gastric and Duodenal Ulcer. Rick Palmer, Kirsner, and Hamann (170) have provided the best and extensive data. The data on healing of gastric ulcer on medical treat with and without x-radiation are shown in Table 150. Their pat

Table 150

Comparison of Healing of Gastric Ulcer with Medical Therapy Alone and with Medical Therapy Plus X-radiation Therapy*

	Medical Treatment Alone		*Medical Treatment Plus X-radiation*	
	Number Cases	*Per Cent*	*Number Cases*	*Per Cent*
Healing	69	60	45	90
No healing	45	40	5	10
Total	114		50	

* Ricketts, Palmer, Kirsner, and Hamann (170).

Duodenal ulcer healed in 89 per cent of 272 cases on medical treatment plus radiation. The percentage for medical treatment alone is not given.

must have had quite intractable gastric ulcer in view of the repor only 60 per cent healed on medical management. Also, healing occ in only 72 per cent of gastric ulcers on the combined treatment w 90 days. Either these ulcers were quite indolent in type, the m management was not sufficiently strict, or the x-ray treatment delay healing in some patients.

Duodenal ulcer healed in 89 per cent of 272 cases on medical trea combined with x-radiation. The ulcer healed in 80 per cent of the within 90 days. The per cent of patients whose ulcer healed on m management alone is not given. However, only 17, or 70 per cent, patients who received the least x-radiation healed and 35, or 95 per of 37 patients who received the largest amount healed. Since the ence is statistically significant, it is reasonable to conclude that the dose of x-ray was of definite benefit in promoting healing. Again, ulcers must have been very intractable in type or the patient did not strict management because it is otherwise unusual for duodenal ul fail to heal in 30 per cent of patients.

ct on Recurrence. Ricketts et al. (170) followed their patients ric ulcer for from one to 10 years. Though the average length of h group was followed is not provided, their results are shown in 51. It is to be noted that the incidence of recurrences was 70 per

Table 151

Incidence of Recurrences in Gastric Ulcer on Medical Management with and without X-radiation*

	Medical Treatment		Medical Plus Radiation Treatment	
	Number	Per Cent	Number	Per Cent
Recurrence	23	70	12	33
No recurrence	10	30	24	67
Total	33		36	

*Ricketts, Palmer, Kirsner, and Hamann (170).

the medically treated patients and only 33 per cent in the patients d x-radiation treatment in addition. In the latter group, 50 per the recurrences occurred within 12 months.

roup of 156 patients with duodenal ulcer was followed for 10 years ceiving x-radiation therapy. Recurrences occurred in two thirds (10 of 15) who received the minimal radiation and in one third 32) of those who received the larger amount. This shows clearly x-radiation therapy was of benefit. It is of interest that 28 per cent ecurrences occurred within one year and 62 per cent within two

ortunately, these authors do not provide the average follow-up on their patients and do not clearly define a recurrence. Thus, it is to compare these results with those of other authors who have edical therapy alone or who have used gastroenterostomy or esection. It would appear from their data that they observed about ent recurrences in an average of 2.5 years.

MENT. The data of Ricketts, Palmer, Kirsner, and Hamann show percentage of patients whose ulcer heals is increased from 70 per en medical therapy alone is used to 94 per cent when appropriate ion therapy is added to the medical therapy. The incidence of ces is decreased from 66 to 32 per cent during a 2.5 year period. ficult to compare the data of these authors with those of Flood our data (see p. 928) because the previous history of recurrences

in their patients is not given. That is, groups of ulcer patients cann compared unless their history prior to treatment is available.

Medical Treatment of Manifest Hemorrhage

Introduction

Since 1900, a controversy has existed regarding the use of morp blood transfusion, early feeding, and surgery in the treatment of mas and, especially, severe hemorrhage from peptic ulcer. Today, it is erally recognized that the management of bleeding peptic ulcer is pr rily medical but sometimes requires the cooperation of the surgeon. has been due chiefly to three factors. One is the importance of preve dehydration; the second is the introduction of the idea of giving l freely by transfusion but relatively slowly by the drip method; the is early feeding.

The ideal management would (1) stop the hemorrhage, (2) pre dehydration, shock, and circulatory failure, (3) treat the ulcer, an treat the anemia.

The methods in general which have been used are: (1) initial fa for 24 to 96 hours, followed by dietary restriction with or without al or antacids, blood transfusions and parenteral fluids, and ice packs t upper abdomen; (2) prompt or early feeding of food, such as milk cream, a soft diet, gelatin, or of almost any ground or puréed food with or without antacids; (3) intubation of the stomach for washing clotted retained blood to prevent nausea, or to lavage the stomach ice water, or to introduce an antacid or food, or intubation of the denum for feeding; (4) surgery (see the next chapter).

Some Treatments Which Have Been and Are Used

In the nineteenth century, severe hematemesis and melena treated by bed-rest, opium or morphine, ice packs on the abd cracked ice to keep the mouth moist, and nothing else by mouth fo to five days (199). This regimen was quite similar to the "starvati "physiologic rest" treatment of peptic ulcer (p. 893). In 1904, Le (165, 200) introduced the regimen of prompt feeding, which consis milk and raw eggs during the first few days and ground meat on the day. He reported a mortality of only 2.1 per cent in a series of 146 c manifest hemorrhage. Physicians disliked the idea of feeding early b that it would maintain the bleeding or induce a recurrence.

Sippy (10, 201), in 1915, used bed-rest, morphine, ice packs, and tuted alkalis with water during the first day. He gave 12 Gm. of C and 4 Gm. of MgO in 30 or 60 cc. of water, which was followed

s with 2.0 Gm. each of $CaCO_3$ and MgO. Then 4.0 Gm. of $CaCO_3$ iven hourly for eight to 10 hours. On the second day, 1.3 Gm. of were given half-hourly and during the night 2.7 Gm. were given . The routine Sippy management was usually started on the third

mpt feeding of patients was initiated again in 1924 by Holmgren nd soon after by Andresen (203), who used gelatin, and by Meu- ht (204), who used most any food as long as it was soft, puréed, , or well masticated.

e *Meulengracht* regimen is as follows:

Blood transfusion on admission if a large quantity of blood has been lost.

Purée diet.

6:00 A.M.	Tea, white bread, butter
9:00 A.M.	Oatmeal with milk, white bread, butter
1:00 P.M. +	Dinner of any of the following foods: ground meat, omelet, fish, broiled chops, vegetables gratin or purée, mashed potatoes, soup, stewed apricots, apple sauce, gruel, rice pudding, tapioca pudding
3:00 P.M.	Cocoa
6:00 P.M.	White bread, butter, sliced meats, cheese, tea, or anything on the dinner menu

Patient to eat as much as he desires.

2 Gm. each of $NaHCO_3$ and $MgCO_3$, 0.25 Gm. of extract hyoscya- mus, and 0.5 Gm. ferric lactate three times daily.

llowing Meulengracht's report in 1935, many clinicians started t feeding with a soft diet with or without the alkalies or antacids, or the routine Sippy on the first day. Others have continued to wait or three days until evidence that hemorrhage has ceased is avail- ither by the blood pressure or the absence of blood in the gastric ge. Kirsner and Palmer (206) start milk and cream and alkalies as tolerated by the patient. They give 30 to 120 cc. of milk or milk eam on the hour and calcium carbonate, 2 to 4 Gm. on the half hour :30 A.M. to 9:30 P.M. Thereafter, during the night, the milk and and alkali are given every two hours. Atropine sulfate 1.0 mgm. is rally or hypodermically every six hours. This plan is continued e stools are negative for occult blood.

ggs (205) in 1909 confirmed the observations of Lenhartz in 25 and reported that relapses occurred less frequently than in a

control group on starvation and barium enemas. Nevertheless, physicians continued to be fearful that early feeding would cause a relapse. As late as results in England up to 1924 were so poor that Robert Hutchison, Chairman of the Section on Surgery, Medicine and Therapeutics, Pharmacology, remarked that there was no medical therapy for hemorrhage since he believed the results would be the same if the patient were put to bed and left alone. This challenge, however, has never been accepted.

Principles of Treatment

Each patient must be treated as an individual with the following principles in mind.

1. Hospitalization. Early hospitalization is recommended because the difficulty of managing such patients is great. Before transportation the patient should be given a sedative and transported in a lying position. Patients in collapse or shock can be given a drip transfusion in the

2. Bed-rest and Reassurance. Bed-rest is obviously indicated. The patient should be made as comfortable as possible. Pillows may be used unless the patient is in collapse (207, 208). The patient should be reassured that bleeding occurs frequently in ulcer patients and that the response to treatment is excellent. The prompt allowance of solid food or water is reassuring.

3. Sedation. In many patients, some barbiturate such as phenobarbital by injection or orally is adequate. In others, opium or morphine with atropine is required to allay anxiety and restlessness (morphine sulphate grains $\frac{1}{6}$ or $\frac{1}{4}$ with atropine sulfate $\frac{1}{150}$ or $\frac{1}{100}$). Morphine and atropine reduce gastric and duodenal tone and motility (209, 210) and decrease the volume of gastric secretion (211). The use of morphine has been objected to because in some persons it may cause vomiting and because, since it decreases gastric and duodenal tone, it may predispose to hemorrhage. The latter objection is hypothetical. The former objection is more realistic. A more important objection, however, is that morphine depresses the respiratory center, which is undesirable in anemia, but the same is true of the barbiturates. Both should be used cautiously, the primary objective being to allay anxiety and restlessness which is more injurious than the objections to the use of either sedative.

4. Prevention of Collapse and Shock: Blood Transfusion. It is more important and easier to prevent shock and collapse than to treat them after it has occurred. Yet there are a great number of authors who warn against this life-saving procedure for fear that it will "blow-out the clot," start a fresh hemorrhage, or cause a reaction. This fear has been based on hypothetic rather than factual considerations.

...on and Kekwick (212) introduced the method of giving trans-
...citrated blood by a continuous drip of 20 to 50 cc. of blood per
...d it has been found that blood may be given at a rate of 8 cc. per
...to 480 cc. per hour for a total of 600 cc. without detecting an
...ble rise in blood pressure, unless the patient is in shock (210, 213).
...son found that the transfusion of 750 cc. of whole blood in the
...who has hemorrhaged severely does not raise the blood pressure
...n 10 mm. and that a rise in blood pressure from 80 to 100 mm. of
...not "blow out" a clot in a small artery (214). In addition, it is
...ll known that, except for ligation, a transfusion, because of its
...ter action, is the most effective means to stop a hemorrhage (215).
...ally, blood transfusions have opponents (216–218), luke-warm or
...advocates (219–221), and enthusiastic supporters (67, 206, 208,
...222–225). Smith (226) quite recently argues for the cautious use
...tions as follows: Reactions occur in 5 per cent of transfusions
...r bloods are cross-matched. Rh antibodies may be produced in
...per cent of women who are Rh negative, and through pregnancy
...only 4 per cent of Rh negative women, therapeutic transfusion
...50 per cent (227). Rapidly given transfusions may embarrass
...heart or start a hemorrhage. Of course, the occasional reaction
...e prevented, but Rh sensitization can be prevented by the proper
...of blood, and a slow transfusion will not embarrass the right
...start a hemorrhage. Some of the earlier authors did not have the
...d the facilities for blood transfusion which have existed since 1938
...e are no crucial data proving that blood transfusion decreases the
...y of hemorrhage from peptic ulcer. A study of a controlled and
...ed group of patients has not been made. And the prevention of
...tion and prompt or early feeding and the liberal use of blood
...ons were all introduced about the same time, namely, between
...d 1940; since which time, the mortality for manifest hemorrhage
...oubtedly decreased.

...ses of severe bleeding of patients in collapse or shock, an emer-
...ansfusion should be given. The establishment of blood banks in
...has resulted in blood being given earlier and more plentifully in
...bleeding peptic ulcer. As a general rule, it is recommended that
...e given when the blood pressure falls below 90 or 100 mm. Hg
...the pulse rate increases above 110 or 120, and the hemoglobin to
...or 8 Gm. per 100 cc. The best and simplest physiologic and
...mptom of the need of blood after the hemorrhage is dizziness
...g on sitting up. Persistent headache, rapid, shallow respiration,
...ter," restlessness difficult to control by other means, and a "gen-
... appearance" are other points indicating the need of blood. In

some cases, an immediate transfusion of from 250 to 500 cc. is indica in others, the blood is best given by drip at 5 to 8 cc. per minute

Inability to maintain the blood pressure and prevent collapse i indication for further transfusion and surgery. Plasma ranks next to w blood but is not a true substitute for whole blood in the treatmen hemorrhage.

5. Prevention of Dehydration: Parenteral Fluids. It should kept in mind that the minimum water requirement of an adult is 8 1000 cc. per day. If visible sweating occurs, the requirement is gre The patient who has lost blood requires even more water because blood volume is restored by the withdrawal of water, electrolytes, proteins from the tissue spaces and cells, unless these substances are plied from outside the body. The need for water is especially evide cause the patient who has lost blood complains of thirst, and is o thirsty than hungry. It should be emphasized, however, that water cannot be retained in the body unless sodium chloride is also avail So the water should be given with sufficient sodium chloride intak make a 0.56 per cent sodium chloride solution.

If the patient can take fluids by mouth, the water should contai or 0.2 per cent sodium chloride, or the extra salt needed could be p in the food. If the patient cannot take food by mouth because of n and vomiting, then the solution, whether given by proctoclysis, h dermatoclysis, or venoclysis, should contain 5 per cent glucose if subcutaneously or slowly intravenously (3 to 5 cc. per minute). Gl should be omitted if the solution is given rectally and the patient doe tolerate it well. The *importance of salt is frequently overlooked;* yet its predisposes to dehydration and alkalosis, especially if alkalis are giv

The patient should receive orally or parenterally 2000 to 3500 water and 10 to 15 Gm. of sodium chloride daily. It should be ke mind that a whole blood, plasma, or serum transfusion is not a subs for water and sodium chloride. Whole blood provides red cells and protein (approximately 7.0 Gm. per 100 cc.). Dried plasma, if r stituted to normality by the addition of distilled water, provides protein and salt (7.0 Gm. of protein and 0.56 Gm. sodium chlori 100 cc.), but the water and salt is not available unless the protein plasma is metabolized. When 5 or 10 per cent glucose solution (n in it) is given, the glucose is oxidized, water without salt is rendered able, and most of the water is excreted in the urine.

Whether fluids should be given intravenously is a controversial tion in the literature. It is argued that if given intravenously the tends to become diluted in regard to red cells and protein concentr This is certainly true if the fluids are given rapidly, but not if given

. It should be noted, however, that fluids given orally or into the
end to dilute the blood less as regards protein than when they are
ntravenously or subcutaneously (228). This is probably due to the
ution of protein by the liver as the fluids flow through it. So, it is
give the fluids by the alimentary tract, when possible. *The patient*
ave fluids, however, because dehydration predisposes to shock,
e, and all the symptoms of blood loss or acute anemia and prevents
intenance and restoration of the circulating blood volume. If
s continue to bleed or relapse once or twice in the face of the ad-
ation of fluids to prevent dehydration and blood to prevent shock
llapse, they should be operated and are in a better condition to
e. Not to prevent dehydration from the start is to invite disaster in
operation becomes the only chance of saving the life of the patient.
e benefit or importance of preventing dehydration cannot be proven
submission of mortality statistics, because prompt feeding, paren-
uids, and whole blood transfusion were introduced about the same
n fact, a most important benefit of prompt feeding is the prevention
dration by the oral intake of fluids. A number of authors of clinical
emphasize the importance of combating dehydration (206–208,
29–231) and few (221, 232) caution against the use of fluids for 24
ours. Some favor the intravenous route of administration (208, 229,
nd others are vigorously opposed to this route (206). It certainly is
cessary to give the fluids intravenously, but a slow intravenous drip
not differ from the rate of subcutaneous absorption.

PROMPT FEEDING: DIET. Almost everyone today agrees that as soon
hemorrhage ceases and nausea and vomiting have disappeared,
nd milk and cream or a soft diet should be fed every two hours, or
es daily. Some believe, and properly so, that milk should be con-
during the night for several days or a week to buffer the nocturnal
on of acid.

ere are really only two important differences of opinion. One per-
o when feeding should be started and the other to whether Meulen-
's diet should be given or whether milk or a soft diet should be given.
roponents of immediate feeding argue as follows: (a) The empty
ch is not "at rest." It manifests some motility and, more important,
crete considerable acid, especially in the case of many ulcer patients.
eding tends to shorten the clotting time of blood, it is reported (233).
rved patients are more likely to relapse than patients promptly fed,
irmed (218). (d) Recovery frequently occurs in ambulatory patients
vere melena without any change in diet; patients suffering pro-
hemorrhage may stop bleeding when fed; and exhaustion from
food contributes to the mortality (204). (e) The presence of food

in the stomach tends to compress the bleeding vessel and favor the formation of a clot (234). (It would be of interest to test this suggestion experimentally in a dog or monkey.) (f) Prompt feeding improves morale. (g) Patients who have had the starvation management for one hemorrhage and the prompt feeding for a second prefer prompt feeding, as might be expected. (h) Food, by diluting blood and promoting peristalsis, relieves nausea and vomiting, which is due to blood clots in the stomach (234, 235).

All of the foregoing arguments may apply to a milk or soft diet as well as to the Meulengracht diet. Several authors who have adopted the Meulengracht regimen omit meat for two or three days.

Some have found that Meulengracht's diet cannot be taken by the severe cases because of nausea and vomiting (219, 220, 236). As a rule, however, nausea and vomiting disappear on the second or third day. In the presence of high-grade pyloric obstruction, this may not be the case, and the patient must be deprived of food for several hours and then transferred to a Sippy regimen or a soft diet.

One may logically inquire: why not start the patient on a Sippy regimen or a soft diet and avoid such a situation? This would seem more rational, unless there is something about the more coarse diet of Meulengracht which tends to stop bleeding. This point, however, need not be strained, since Meulengracht points out that prompt feeding and not the composition of the diet is the important aspect of his regimen (204).

We believe that prompt feeding should be practiced, using the Sippy plan of feeding or a soft diet every two hours, and that the feedings should be continued during the night at two hour intervals for several days. If nausea and vomiting persist, orally administered food should be replaced by some pleasant antacid for the control of the free acid in the fasting gastric secretion. Glucose should be given parenterally to prevent ketosis.

We believe that it is important to control the gastric acidity day and night in the presence of nausea and vomiting, if at all possible. Sometimes chloretone (0.3 to 0.5 Gm.) will control vomiting when other procedures fail. A good drug to control vomiting is needed because nausea and vomiting are the stumbling block to oral feeding and the control of gastric acidity. Intravenous feeding does not control gastric acidity and may stimulate it (237, 238); in addition, it has the same objections as those which have been offered against intravenous fluids.

Vitamin K is clearly indicated in those patients with prolonged prothrombin time. Since the prothrombin may be low and time is required to make the determination, we recommend that it be given every four hours intramuscularly until the prothrombin has been determined. Vitamin C, rutin, and Vitamin P (hespiridin methylchalcone, citrin) may be of value in hemorrhage from erosive gastritis.

ALKALIS AND ANTACIDS. If alkalis and antacids are ever indicated protection of a peptic ulcer, they are indicated when the ulcer is g. If given, they should be given with plenty of water and adequate prevent dehydration and alkalosis.

vertheless, we find the same difference of opinion regarding the use lis and antacids in bleeding peptic ulcer as is encountered in their nonbleeding ulcer. Many have used the Sippy regimen as described Others report favorable results with tribasic magnesium or calcium ate (231, 239) used in place of the soluble alkalis. Others use alkalis ing to some other plan of their own, such as after preliminary tion (232), only for pain (207, 208), and between feedings (219). thers use food chiefly to buffer acid (220, 240).

some cases of hematemesis due to gastric bleeding, the bleeding from acute ulcers in atrophic gastric mucosa. Some of these cases are ine-fast and hence alkalis are not needed (241, 242).

INTUBATION FOR FEEDING OR ANTACID MEDICATION. The manage- of bleeding peptic ulcer by duodenal feeding was recommended by n (243). Very good results have been reported by Rafsky (236, 244) e 152).

Table 152

SHOWING RESULTS USING INTUBATION IN PATIENTS WITH BLEEDING PEPTIC ULCER

Author	Size of Tube	Material Introduced	Number Cases	Number Deaths	Per Cent Mortality
(244)	Duodenal	Food	40	0	0
(245)*	Duodenal	"	28	0	0
an (246)	Stomach	$Al(OH)_3$ Food	144	3	2.0
et al. (236)	Duodenal	Food	34	1	2.9
			246	4	1.6
ola (266)†	Stomach	Suction and fasting	84	15	17.6

ed tube to lavage stomach for first day and then gastric and duodenal feeding; hoplastic substance was introduced into the stomach after the first lavage. The are assumed to be peptic ulcer, the author does not state.
lected only very severe cases in shock, none of whom could eat early.

er (245) intubated the stomach in hematemesis to wash out the clots and to introduce a thromboplastic substance. After the first used the tube for gastric or duodenal feeding.

Winkelstein continuous alkaline milk drip has been used and

insures continuous neutralization of free acidity (124). Woldman and others (222, 246) have given $Al(OH)_3$ cream by mouth every hour until vomiting ceases and then by continuous drip along with a soft diet every two hours.

Though the method of continuous drip is the best way to control gastric acidity and is exceedingly well tolerated for a few days by some patients, it is likely to produce vomiting in other patients. Fatal hemorrhage has coincidentally occurred after the passage of a Levin tube (247).

9. Attention to Bowels. Mineral oil or MgO is used and is frequently necessary when calcium carbonate or $Al(OH)_3$ is used. The use of enemata during the first few days has been interdicted by some because of the fear of starting a hemorrhage (206, 218). Prompt feeding usually prevents the need of enemata, but Meulengracht uses cascara as an aperient.

10. Treatment of Anemia. Most physicians prescribe iron in some form; when given in adequate amounts (0.5 Gm. ferric lactate t.i.d.), it has been found to increase the rate of regeneration of hemoglobin in ulcer patients who have bled considerably (248).

11. Miscellaneous. Snake venom and various hemostatic or thromboplastic substances have been used, but none have been found to be of value. Epinephrine (adrenalin) has been administered orally, the dose being 5 to 10 cc. of the 1 to 1000 solution diluted in 10 or 25 cc. of water. Vitamin K is definitely indicated in those cases with low prothrombin value. Thromboplastin prepared from brain tissue has been given orally. Thrombin has been given orally and subcutaneously. The use of fibrin impregnated with a thrombin solution has been suggested. None of these procedures can be rationally applied to stop a hemorrhage from an open artery. They may be of some use in the hemorrhage of erosive gastritis; this would be very difficult to prove, however.

Evaluation of Different Methods of Medical Treatment of Hemorrhage in Peptic Ulcer

No one knows better than we the difficulty inherent in any attempt to evaluate the various methods of medical management by comparing mortality statistics. This is due to many variable factors; namely, method of collection, method of presentation, and intrinsic variations between different series of small or large groups of patients, such as accuracy of diagnosis, age of the patient, site of the ulcer, social status of the patients, extent of ready availability of hospital services, existence of other disease, and necessity of varying or individualizing the treatment in many patients.

In Table 153 are found the data of authors who have used the Meulengracht regimen and those who have used the plan of prompt feeding with a soft diet. In Table 154 are found the data of authors who have used

Table 153

MORTALITY FROM HEMORRHAGE FROM PEPTIC ULCER ON PROMPT-FEEDING REGIMENS

Author	Diet	Number Cases		Deaths			
				Number		Per Cent	
		Gross	Net*	Gross	Net	Gross	Net
Meulengracht (204, 235)	Meulengracht	1031	1021	26	16	2.5	1.6
Gram (267)	"	106	104	4	2	3.8	1.9
Gubergrits (268)	"	15	15	0	0	0	0
Boyd et al. (269)	"	15	15	0	0	0	0
Crohn et al. (219)	"	23	23	2	2	8.7	8.7
Barnes (270)	"	30	30	0	0	0	0
Alder (271)	"	40	40	1	1	2.5	2.5
Chasnoff (272)	"	21	21	1	1	4.7	4.7
Mayer et al. (273)	"	130	126	6	2	4.6	1.6
Rafsky et al. (236)	"	39	35	4	0	10.3	0
Schiff (220, 274, 275)	"	160	154	11	5	6.83	3.1
Eichorn (276)	"	38	38	0	0	0	0
Strawn (277)	"	32	32	0	0	0	0
Chaikin et al. (278)	"	30	29	1	0	3.3	0
Emery (279)	"	36	34	2	0	5.5	0
McMillan (280)	"	15	12	3	0	2.0	0
Bohmansson (281)	Food early	214	214	11	11	5.0	5.0
Total A†	..	1975	1943	72	40	3.6	2.1
Jones‡ (282)	Bland and soft	615	601	48	34	7.8	5.1
Witts‡ (207)	"	24	24	0	0	0	0
Scott‡ (283)	"	60	59	3	2	5.0	3.3
Lenhartz (165, 200)	"	146	146	4	4	2.1	2.1
Andresen (203)	Gelatin	120	117	6	3	5.0	2.5
La Due (284)	"	79	79	5	5	6.3	6.3
Browne et al. (222)	Soft and bland	15	15	2	2	13.3	13.3
Woldman (246)	"	144	144	3	3	2.1	2.1
Nicholson et al. (234)	"	32	31	1	0	3.1	0
Matzner et al. (285)	"	35	35	0	0	0	0
Freed et al. (286)	"	23	23	0	0	0	0
Segal et al. (287)	"	35	34	2	1	5.7	3.0
Clemmesen (288)	"	273	260	20	7	7.3	2.7
Turnbull et al. (289)	"	10	10	0	0	0	0
Rasberry et al. (290)	"	43	41	3	1	7.0	2.4
Rafsky et al. (236)	"	64	64	1	1	1.6	1.6
Hesser (223)	"	304	304	15	15	4.9	4.9
Eads (224)	Bland	129	129	3	3	2.3	2.3
Fraser et al. (291)	"	165	165	7	7	4.2	4.2
Costello (247)	"	73	73	3	3	4.0	4.0
Lineberry et al. (292)	Sippy, early	38	38	1	1	2.6	2.6
Kirsner et al.§ (206)	"	230	227	8	5	3.5	1.3
Brown¶ (67)	"	201	198	4	1	2.0	0.5
Total B	..	2858	2817	139	98	4.9	3.5
Baker‖ (293)	Soft	576	557	77	58	13.4	10.0

* Net represents the gross figure minus deaths not due to exsanguination.

† If Meulengracht's cases are omitted, the number of cases gross 946 and net 922; the deaths gross 46 and net 24; the percentage gross mortality is 4.1 and the net mortality is 2.6.

‡ They used the regimen of Witts, which emphasizes the prevention of dehydration.

§ Six of eight deaths occurred in 41 cases starved more than one day.

¶ Brown recommends that the Sippy regimen be started immediately but does not state that he did so in the 201 cases reported.

‖ Baker used Witts' plan but did not start prompt feeding in severe cases. His patients came from an industrial population during the war and are weighted with patients above 60 years of age.

Table 154

MEDICAL MANAGEMENT OF HEMORRHAGE FROM PEPTIC ULCER WITH PRELIMINARY FASTING PLUS VARIOUS TYPES OF SO-CALLED "CONSERVATIVE MANAGEMENT" OR "MEDICAL MANAGEMENT"

Author	*Treatment*	*Number Cases*		*Deaths*			
		Gross	*Net*	*Number*		*Per Cent*	
				Gross	*Net*	*Gross*	*Net*
Manheim (294)	Initial fasting with modified Sippy	94	94	4	4	4.2	4.2
Rafsky et al. (236)	Sippy	271	255	30	14	11.0	5.2
Browne et al. (222)	"	37	37	1	1	2.7	2.7
Emery & Monroe (180)	"	384	384	20	20	5.2	5.2
Lynch (232)	"	31	31	4	4	12.9	12.9
Total A	..	817	801	59	43	7.2	5.3
Christiansen (216)	Initial fasting with soft diet	289	287	23	21	7.9	7.8
Hellier (295)	"	202	196	36	30	17.8	15.3
Davies & Nevin (296)	Ditto, some transfusions	385	385	79	79	20.5	20.5
Boyd et al. (269)	Initial fasting, soft diet	30	30	6	6	20.0	20.0
Hurst & Ryle (217)	"	258	252	10	4	3.9	1.6
de la Viesca (297)	"	130	130	9	9	6.9	6.9
Paterson (298)	"	120	120	4	4	3.3	3.3
Goldman (221)	Ditto, with some alkalies and transfusions	349	332	56	39	15.0	11.7
Chiesman (305)	Initial fasting with some alkalies	191	191	46	46	24.1	24.1
Total B	..	1954	1923	269	238	13.7	12.2
Blackford* (299)	Conservative	36	34	6	4	16.8	11.8
Enocksson (300)	"	105	105	14	14	14.0	14.0
Crossan (229)	"	73	73	11	11	14.0	14.0
Burger et al. (306)	"	137	137	31	31	22.6	22.6
Aitken (307)	"	234	234	20	20	8.5	8.5
Wilkie (301)	"	249	249	29	29	11.6	11.6
Bohrer† (302)	"	182	182	14	14	7.7	7.7
Thorstad (308)	"	138	138	19	19	13.7	13.7
Total C	..	1154	1152	144	142	12.5	12.3
Bulmer (303)	Conservative, transfusions	576	576	60	60	10.4	10.4
Cullinon et al. (218)	"	101	101	15	15	14.8	14.8
Holman (304)	"	161	161	21	21	13.0	13.0
Total D	..	838	838	96	96	11.4	11.4

* Massive hemorrhage only.

† Includes a group of 80 cases classified as massive hemorrhage in which the mortality was 17.5 per cent. He advocated washing out the stomach.

Table 155

SHOWING THE AVERAGE OF RESULTS REPORTED WITH DIFFERENT TYPES OF MEDICAL REGIMENS FOR MANIFEST BLEEDING OF PEPTIC ULCER

Therapy	*Number of Cases*		*Deaths*				*References*
	Gross	*Net**	*Number*		*Per Cent*		
			Gross	*Net*	*Gross*	*Net*	
Prompt feeding, Meulengracht	1975	1943	72	40	3.6	2.1	219, 235, 236, 267–273, 275–281
A. Excluding Meulengracht's data	944	922	46	24	4.8	2.6	219, 236, 267–273, 275–281
Prompt feeding of soft diet or Sippy	2858	2817	139	98	4.9	3.5	67, 165, 200, 203, 206, 207, 222–224, 234, 236, 246, 247, 282–292
Initial fasting of 24–72 hr. + Sippy	817	801	59	43	7.2	5.3	
Baker's data†	576	557	77	58	13.4	10.0	293
Initial fasting + soft diet	1954	1923	269	238	13.7	12.2	216, 217, 221, 269, 295–298, 305
"Conservative"‡	1154	1152	144	142	12.5	12.3	229, 299–302, 306
Conservative + transfusions	838	838	96	96	11.4	11.4	218, 303, 304
A + B + C + D + E + F + G	10307	10168	858	716	8.3	6.9	

χ^2 of difference between 2.1 per cent (A) and 2.6 per cent (AA) is not significant.
χ^2 " " " 3.6 per cent (A) and 4.8 per cent (AA) is not significant.
χ^2 " " " 2.1 per cent (A) and 3.5 per cent (B) = 8.4 and is significant.
χ^2 " " " 3.6 per cent (A) and 4.9 per cent (B) = 4.1 and is significant.
χ^2 " " " 2.6 per cent (AA) and 3.5 per cent (B) (0.3) is not significant.
χ^2 " " " 4.8 per cent (AA) and 4.9 per cent (B) is not significant.
χ^2 " " " 2.6 per cent (AA) and 5.3 per cent (C) is significant.
χ^2 " " " 4.8 per cent (AA) and 7.2 per cent (C) is significant.
χ^2 " " " 3.5 per cent (B) and 5.3 per cent (C) is not significant.
χ^2 " " " 4.9 per cent (B) and 7.2 per cent (C) = 8.+ and is significant.

* Net refers to patients who were believed to have died only from exsanguination.

† Baker's data is considered separately because prompt feeding of a soft diet was ot given to severe cases and his group is weighted with patients over 60 years.

‡ "Conservative" treatment is medical treatment, the type of which is not clearly ecified by the author; it generally means initial fasting, little attention to the adminisation to fluids, no or few and small blood transfusion, deep sedation, and fasting for o to five days.

initial fasting with the Sippy regimen, initial fasting with a soft diet, an a conservative management with and without transfusions. The averag of all the data with the different plans are summarized in Table 155. will be noted that the prompt feeding regimens have been associated wit a lower mortality than that of initial fasting regimens. A study of th references from which the average results are derived will indicate that th results with prompt feeding represent recent studies. A closer study of th articles will reveal that one cannot be certain from these reports wheth prompt feeding, the prevention of dehydration, or the more liberal use blood transfusion is involved. The important point is that the data sho that *the mortality from medical management has definitely improved in recent yea and that this has been associated with the prevention of dehydration, the liberal use blood transfusions, and the institution of the feeding of a soft diet as soon as tolerat by the patient.* Either medical management has improved or bleeding pept ulcer has become more mild.

As a splendid example of the effect of improved methods for the ma agement of bleeding peptic ulcer, the statistics from a single clinic ove period of years is shown in Table 156. Though the introduction of "i

Table 156

MORTALITY FROM MANIFEST HEMORRHAGE DUE TO PEPTIC ULCER AS RELATED TO INTRODUCTION OF NEW METHODS AND LESSENED NEED FOR SURGERY, WHEN A GOOD CONSERVATIVE MANAGEMENT IS AVAILABLE*

Treatment	*1929–1938*		*1939–1945†*		*1929–1945*	
	Number Cases	*Per Cent Deaths*	*Number Cases*	*Per Cent Deaths*	*Number Cases*	*Per C Dea*
Medical	166	6.0	214	5.0	380	5
Surgical	140	13.0	19	5.2	159	11

* Bohmansson (281).

† Early feeding, blood transfusions, and fluids were introduced into the me and surgical therapy in 1939.

proved methods" did not significantly change the mortality rate of so medically managed patients, they did decrease the need for surgical in vention and reduced surgical mortality.

In Table 157 are shown data of a relatively large number of pati treated by the same physician with four different medical methods. W the deaths ascribed to exsanguination alone are considered, a signifi difference in the mortality is not observed. The methods, however, do vary much as regards the prevention of dehydration, early feeding, blood transfusion. However, when the mortality statistics from the s

Table 157

RESULTS WITH DIFFERENT MEDICAL TREATMENTS*

Diet	Total Cases	Deaths All Causes		Deaths due to Bleeding Only	
		Number Cases	Per Cent	Number Cases	Per Cent
itial (Sippy) fasting	271	30	11.0	14	5.2†
Ieulengracht‡	39	4	10.3	2	5.1
uodenal intubation and bleeding	34	1	2.9	1	2.9
ombined§	64	1	1.6	1	1.6†

* Rafsky and Weingarten (236).

† The difference between 5.2 per cent and 1.6 per cent is not statistically significant ($\chi^2 = 1.53$); the difference between 11.0 per cent and 1.6 per cent is significant.

‡ The diet could be followed without interruption in 26. It had to be discontinued n 13 due to recurrence of hemorrhage in seven and for other reasons, such as pain in ree and vomiting in three.

§ Food withheld for 24 hours or as long as bleeding continued; venoclysis and blood ansfusion; milk and cream, then soft diet and alkalies or $Al(OH_3)$.

Table 158

MORTALITY FROM MANIFEST BLEEDING IN PEPTIC ULCER AS RELATED TO PROMPT FEEDING AND STARVATION REGIMENS

Author	Prompt Feeding			Fasting		
	Number Cases	Number Deaths	Per Cent Mortality	Number Cases	Number Deaths	Per Cent Mortality
Ieulengracht (309)	119	5	4.0	75	11	15.0
hasnoff et al. (272)	21	1	4.8	72	8	11.1
chiff (220, 274)*	160	11	6.8*	78	20	25.6
oyd et al. (269)	15	0	0	30	6	20.0
Total	315	17	5.4	255	45	15.7
ullinan et al. (218)	..	..	..	105	19	18.1
nes, F. A. (282)†	530	42	7.9†	..	..	..
Ieulengracht (235)‡	..	..	1 to 2‡	..	..	8–10‡

* If corrected for patients dying only of exsanguination, the figure is 3.1 per cent.

† If corrected for patients dying only of exsanguination, the figure is 5.1 per cent.

‡ Patients in Denmark may get to hospitals sooner than those in the United States nd England.

The Cullinan and Price data are from 1925 to 1929; the Jones from 1940 to 1947.

clinic are compared where the starvation and prompt feeding regim varied considerably, as shown in Table 158, it is found that prompt feedi has a significantly lower mortality than the old starvation regimen, whi paid no attention to the prevention of dehydration. *These data consti strong evidence that the prevention of dehydration is very important*, which, howev does not minimize the life-saving attributes of a whole blood transfusi in severe hemorrhage.

Comment

If the internist receives a patient who is not in a state of irreversi shock, the least the internist should attempt to do is to manage the pati so that the patient constitutes a fair to good surgical risk. To do t adequate fluids and whole blood are required.

Fifty per cent of those patients who usually are referred to surg would die if medical management had been continued, whereas only per cent die if operated by gastric resection (Table 160, Chapter 1 If dehydration is prevented and the circulating blood volume is ma tained by blood transfusions, should the mortality be more than 5 per c even with a wide open artery? It has been said that a surgeon wh operative mortality is more than 5 per cent in cases of elective ga surgery should not be selected to operate on patients with bleeding pe ulcer (249).

The indications for surgery will be discussed in the next chapter.

Medical Treatment of Perforation

Acute Perforation. The treatment of this condition is chiefly surg and will be discussed in the next chapter.

Acute Perforation with Spontaneous Closure. Intragastric tinuous hydrostatic suction should be used for two or three days parenteral fluids and feeding. Continuous intragastric drip should be used. If the patient does not tolerate the tube, then the patient sh be given either water with alkalies or antacid orally, as in the case bleeding ulcer, to neutralize acid secretion, or the patient should be g nothing by mouth for 48 to 72 hours. Then, the Sippy diet or freq feedings of a soft diet should be instituted as in the treatment of a "chr perforation" or a penetrating ulcer.

Chronic Perforation or Penetrating Ulcer. Bed-rest is defin indicated. A continuous 24 hour gastric drip using an alkali or an (p. 901) should be used for three to five days, followed by frequent fee with an antacid hourly from 7:00 A.M. to 9:00 P.M. and at two h intervals during the night for seven to 14 days, depending on the

ndings. If the tube is not tolerated by the patient, then the feedings and ntacid should be given orally on the hour night and day for 10 to 14 days r longer, depending on the x-ray findings.

Treatment of Obstruction or Gastric Retention

The only way to determine to what extent gastric retention is due to pasm and edema or to cicatrization is to treat the patient medically.

If the patient is not vomiting much, ordinary medical management of peptic ulcer for a period of several weeks or months will indicate the extent of cicatricial obstruction.

If the patient has been vomiting considerably, then the dehydration nd hypochloremia and alkalosis should be treated immediately with parenteral fluids. Parenteral feeding may be instituted. The stomach is vacuated morning and evening, or more frequently if necessary. Some se continuous suction. The chloride lost by aspiration should be estimated nd replaced with sodium chloride parenterally. Alkali or antacid may be iven for pain. The anemia, if the hemoglobin is below 10 Gm. per 100 cc., s best treated with a whole blood transfusion. After two or three days, hen the five or six hour secretion has decreased to less than 250 cc., the ippy regimen with an aspiration at 10:00 P.M. may be instituted. At irst, it is advisable to dilute the milk and cream and to bring it to a boil to lecrease the firmness of the curds formed from the milk. This may be done lso by adding some gruel or malted product to the milk, or diluted uttermilk or thin gelatin may be used.

In patients who have a marked retention and a history that it has been present for several months, a longer period than three days of parenteral eeding with frequent aspiration may be required to cause a return of postural tone to the gastric musculature so that it will manifest normal peristaltic activity, which is necessary for normal gastric evacuation. The dea is to keep the stomach "decompressed" until its elongated and atonic nuscle fibers are able to resume the much shorter length of those of the ormal fasting stomach and then to give a thin pabulum in small quanities at frequent intervals so as not to redistend the stomach. When this is one for several weeks, a remarkable decrease in the extent of retention requently occurs. Even if the need of surgery should become evident, the tomach should be "decompressed" for a period, especially if a gastroenterostomy is to be performed.

Summary

Chapter 24 will provide a summary of the more important observations made in this chapter.

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OUTLINE OF CHAPTER 23

Surgical Therapy of Peptic Ulcer

I. INTRODUCTION
II. VARIATION IN PERCENTAGE OF PATIENTS REFERRED FOR SURGERY
III. INDICATIONS FOR SURGICAL THERAPY
  A. OBSTRUCTION
  B. HEMORRHAGE
    1. Acute "Massive" Hemorrhage
    2. Chronic Recurrent Hemorrhage
    3. Subtotal Gastric Resection
    4. Elective Surgery in Convalescent Period after Acute Hemorrhage
  C. PERFORATION
  D. INTRACTABLE PAIN
  E. GASTRIC ULCER SUSPECTED TO BE CARCINOMA
IV. PRINCIPLES OF SURGICAL THERAPY OF PEPTIC ULCER EXCLUDING ITS COMPLICATIONS
  A. REDUCTION OF GASTRIC ACIDITY
    1. Reduction of Secretory Capacity of Gastric Glands
      a. Resection of Parietal Cell Area
      b. Total Gastrectomy
      c. Fundusectomy
      d. Partial Gastrectomy
      e. Subtotal Gastrectomy
      f. Ligation of Gastric Arteries or Blood Vessels
      g. Reduction of Stimulation of Parietal Cells
      h. Removal of Pars Pylorica: Pylorectomy
      i. Reduction of Gastric Emptying Time
      j. Vagotomy
    2. Facilitation of Enterogastric Regurgitation
  B. REST OF ULCERATED PART BY DIVERSION OF ACID CHYME, IMPROVEMENT OF EMPTYING, AND RELIEF OF STASIS
    1. Diversion of Acid Chyme of Gastric Contents
  C. A SHORT JEJUNAL LOOP
  D. AVOIDANCE OF GASTROENTEROSTOMY EN-Y AND ENTEROSTOMY

E. REMOVAL OF ULCER-BEARING TISSUE
F. COMMENT

IMMEDIATE MORTALITY RATE OF ELECTIVE OPERATIONS FOR PEPTIC ULCER

A. INTRODUCTION
B. MORTALITY RATE OF PYLOROPLASTY AND GASTROENTEROSTOMY
C. MORTALITY RATE OF GASTRIC RESECTION
    1. Factors which Influence Mortality Rate
        a. Site of Ulcer
        b. Age
        c. Type of Operation
D. MORTALITY RATE OF VAGOTOMY
E. MORTALITY RATE OF FUNDUSECTOMY AND VASCULAR LIGATION
F. SUMMARY

LATE RESULTS OF OPERATIONS ON THE STOMACH

A. INTRODUCTION
B. EXCISION OF THE ULCER
C. GASTROENTEROSTOMY
    1. Gastroenterostomy for Duodenal Ulcer
    2. Gastroenterostomy for Pyloric Ulcer
    3. Gastroenterostomy for Gastric Ulcer
    4. Gastroenterostomy for Peptic Ulcer
    5. Factors which Influence Results After Gastroenterostomy
        a. Pyloric Exclusion
        b. En-Y and Enteroenteroanastomosis
        c. Anterior and Posterior Gastroenterostomy
        d. Selection of Patients
        e. Sex
        f. Age
D. PYLOROPLASTY FOR PEPTIC ULCER
E. GASTRIC RESECTION
    1. Introduction
    2. Gastric Resection for Duodenal Ulcer
    3. Gastric Resection for Gastric Ulcer
    4. Gastric Resection for Peptic Ulcer
    5. Factors Influencing Recurrence Rate and Percentage of Satisfactory Results After Resection
        a. Size of Resection
        b. Choice between Billroth I and Billroth II Gastric Resection
        c. Length of Jejunal Loop

d. Method of Handling Nonresectable Duodenal Ulcer
e. Various Alternatives to a Typical Gastroduodenal Res
f. Gastric Resection with Pyloric Exclusion
g. High-lying Gastric Ulcer
h. Obstructing Ulcer
i. Enteroenterostomy and En-Y Anastomosis
j. Sex
k. Age

6. Cause and Treatment of Unsatisfactory Results after G enterostomy and Gastric Resection
   a. Anastomotic and Recurrent Ulcer
      (1) Medical Therapy of Anastomotic Ulcer
      (2) Conservative Operative Procedures for Anast Ulcer
      (3) Gastric Resection for Anastomotic Ulcer
      (4) Gastric Resection with Pyloric Exclusion for Ulcer
      (5) Vagotomy for Anastomotic Ulcer
   b. Hemorrhage
   c. Postcibal or Postprandial Distress
      (1) Incidence
      (2) Symptoms
      (3) Etiology
      (4) Treatment
   d. Food Intolerances
   e. Weight Changes after Gastric Resection and Gastr ostomy
   f. Anemia Following Gastric Resection and Gastr ostomy
      (1) Pernicious Anemia
      (2) Hypochromic Anemia
   g. Other Deficiencies

F. RESULTS OF VAGOTOMY FOR PEPTIC ULCER

1. Introduction
2. Rate of healing
3. Vagotomy for Duodenal, Gastric, Peptic, and Anast Ulcer
4. Factors Affecting Results of Vagotomy
   a. Transthoracic vs. Transabdominal Vagotomy
   b. Selection of Patients
5. Cause and Treatment of Unsatisfactory Results Fo Vagotomy
   a. Recurrences
   b. Disturbances of Motility
   c. Weight and Anemia Following Vagotomy

G. RESULTS OF FUNDUSECTOMY AND VASCULAR LIGATION
H. DIET AFTER GASTRIC OPERATIONS
I. REPORTING LATE RESULTS

TREATMENT OF PERFORATED PEPTIC ULCER

A. INTRODUCTION
B. MORTALITY
C. SIGNIFICANT FACTORS INFLUENCING PROGNOSIS AND MORTALITY
   1. Age of Patient
   2. Sex of Patient
   3. Site of Lesion
   4. Time Elapsing between Perforation and Treatment
   5. Pre- and Postoperative Care
   6. Chemotherapy and Antibiotics
   7. Drainage of the Abdomen
   8. Choice of Anesthesia
D. CHOICE OF OPERATION
   1. Mortality Rates of Different Operations for Perforated Peptic Ulcer
   2. Recurrence after Perforation
      a. Simple Closure
   3. Factors Which Affect Recurrences after Perforation and Simple Closure
      a. Diet
      b. Age
      c. Duration of Previous Ulcer History
   4. Late Results of Pyloroplasty or Gastroenterostomy Combined with Simple Closure for Perforated Peptic Ulcer
   5. Late Results of Gastric Resection for Perforated Peptic Ulcer
E. NONOPERATIVE TREATMENT OF PERFORATED PEPTIC ULCER
   1. Introduction
   2. Elective Nonoperative Treatment of Early Perforation
      a. Essentials of Elective Nonoperative Treatment
      b. Results

TREATMENT OF HEMORRHAGE

CHAPTER 23

Surgical Therapy of Peptic Ulcer

Introduction

The surgical treatment of peptic ulcer is reserved for pati have not responded to medical therapy. The major problems o therapy are the proper selection of patients for treatment and o of an operation which will offer a reasonable assurance of cur too great an operative mortality or too high an incidence of post complications.

The indications for operative treatment are considered to be foration, (b) organic obstruction, (c) some cases of hemorrhage which is intractable to medical measures, and (d) gastric ulcers of malignancy. The indications for surgical therapy have not alw so definitely limited. In fact, the choice of medical or surgical t peptic ulcer has gone through several periods of variation in va

The treatment was conceded to be medical until the succ formance of a pylorectomy for cancer by Billroth in 1881 and a enterostomy for cancer by Wölfler in 1881 (1). Following these operations, surgeons began to treat some cases of ulcer of the s operation (2). Rydygier performed the first gastroenterostomy ulcer in 1884 (1).

Beginning shortly after 1900, and particularly after Moynih sized the frequency of occurrence and developed the diagnosis o ulcer, some surgeons advocated that every chronic ulcer of th and duodenum should be treated by operation (3, 4). Others lieved that medical therapy should be given a trial but operat high percentage of patients when they did not respond pr medical measures or when they had a recurrence. However, s or since the introduction of an improved medical manageme accumulation of statistics on the occurrence of postoperative syndromes, most internists and surgeons have agreed that surg be reserved for patients who have not responded well to medical ment. Since then, there has been a gradual trend toward op fewer patients and using more radical operative procedures. T tions for operation have frequently been classified as absolute or

...ver, the indications are always relative. This is even true for ...n, which may be acute or "intractable" and treated by non- ... methods early and late.

...mphasizes that the indications for surgical therapy must always ...ered in relation to the conditions presented by each patient.

...ation in Percentage of Patients Referred to Surgery

...e foregoing reason, and because of the existence of differences ...oint of some surgeons and internists and because of the dif-

Table 150

...ons for Surgery, Showing That More than One Complication ...quently Is the Reason for Referring the Patient to Surgery

Indications	Garvin (73)				Counsel and Hinton (13)		Kenning* (44)	
	Duodenal Ulcer		Gastric Ulcer		Duodenal Ulcer		Duodenal Ulcer	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
...pain alone	65	19.3	20	22.2	48	46.1	146	56
...e alone	9 (3)*	2.7	3 (1)*	3.3	2	1.0	13	5
...a alone	3	0.9	..	..	1	1.0	5	2
...orrhage	77 (16)*	23	6 (4)*	39	37	36.5	96	37
...iting	46	14.1	19	21.1	..	..	..	..
...ruction	41	12.5	6	6.6	7	6.6	..	..
...ing, & hemorrhage	47 (3)*	14.4	10 (2)*	11.1	..	..	..	..
...rrhage, & obstruction	38 (3)*	11.6	5	5.5	3	2.8	..	..
...degeneration					1	1.0	..	..
...orrhage, & malignant ...ation	..	..	..	..	1	1.0	..	..
...uction, & possible ma- ...generation					3	2.8		
...ive hemorrhage	..	..	..	..	1	1.0	..	..

...y patients operated upon as emergency for acute massive hemorrhage.

...the extent of complications in groups of patients which consult ...physicians and clinics, it is not surprising that the percentage ...referred for surgery differs between clinics. For example, Brown ...is associates have referred to surgery 10.6 per cent of 1500 ...ated by them since 1930. At the Lahey Clinic, 6.9 per cent of

8380 peptic,* 6.1 per cent of 7844 duodenal, and 19.3 per cent of 53 ulcers were referred to surgery (8). At the Mayo Clinic (9), fr 65 per cent of patients with gastric ulcer seen yearly since 1935 h treated surgically, but surgical treatment for duodenal ulcer from 26 per cent in 1930 to 12 per cent in 1944. Of 995 duoden patients seen by Hinton and Church (10, 11), 14 per cent were s to surgery. Of 1515 patients with complicated duodenal ulcer by Sanders (12), 29 per cent were submitted to surgery.

The major cause of the difference in the reports dealing subject is the extent to which *intractable pain and frequency of recu* considered to be indications for surgery (Table 159). However, distressing complications of peptic ulcer are frequently multiple mately one half of the surgically treated patients have more complication when submitted to surgery.

Indications for Surgical Therapy

Obstruction

Gastric retention occurs in about 25 to 30 per cent of gastric denal ulcers. However, only 20 per cent of gastric ulcer pati retention and about 10 per cent of duodenal ulcer patients with will have a significant degree of organic obstruction. One ma the gastric retention of the remaining cases to disappear on therapeutic management.

Hinton (10) believes that pyloric obstruction without pain w respond to medical therapy and that surgery is not indicate absence of pain. In our experience, surgery for pyloric obstru been indicated more frequently in the absence than in the pr typical ulcer distress.

Experience teaches that every patient with pyloric obstructi be given a trial on strict medical management. If the degree retention does not decrease and the general condition of th including body weight, does not improve, surgery is indicated.

The indication for the surgical management of an hourglass is identical with that of obstruction of the pylorus.

Hemorrhage

Surgical therapy may be indicated as an emergency pro acute massive hemorrhage, or a hemorrhage which fails to

* Throughout this Chapter, the word "peptic" is used to designat duodenal and gastric, as well as anastomotic ulcers in some instances

s on medical management, or as an elective procedure in the con-
at period in patients who are subject to recurrent hemorrhages.
"Massive" Hemorrhage. Most cases of massive bleeding of
ulcer will respond to medical therapy and whole blood transfusions.
cases, probably 5 per cent, will bleed to death in spite of the best
l therapy. It should be recalled that some patients die of coro-
g disease and not exsanguination. Also, some authors believe that
cating disease bars the attempt to save life by an operation (14, 15,
ough Stewart et al. 116) do not consider most complicating diseases
raindication to an operation.
ergency surgical intervention should be seriously considered when
ical condition of the patient and the blood pressure and other
indicate that hemorrhage is continuing or when a relapse occurs
dical management in the hospital. This is most likely to occur in a
over 45 or 50 years of age. The mere massiveness of a hemorrhage
ot constitute an indication for surgery.
e diagnosis of peptic ulcer should be established before surgical
ion is undertaken. This recommendation is supported by the fact
cases of hematemesis and melena are not due to bleeding ulcer
at the mortality of medical management is quite low in "x-ray
" cases and bleeding from gastritis (14, 17, 18, 420). It is in the
in which the diagnosis is not certain that the Hampton technic of
raphy and early gastroscopy may be indicated, provided whole
is readily available for transfusion.
eration is indicated when a peptic ulcer continues to bleed in spite
best medical management because the chances are good that the
the patient may be saved. This cannot be proven by the comparison
mortality rate of the usual series of medically treated with surgically
cases. Such a comparison is unjustified because the operation is
undertaken only where it appears that the patient will bleed to
and often the internist has handled the case so that it constitutes
bad surgical risk. In order to obtain some data on this point, we
d from the literature those more recent articles which provided
on patients who continued to bleed in spite of good medical
ment, some of whom were treated surgically and in others of whom
l management was continued. The data are shown in Table 160.
ults indicate that 50 per cent of the patients in whom medical
ment was continued, and only 18.5 per cent on whom surgery
rformed, died. The difference is significant, the chief weakness of
a being the lack of information on the average age of both groups.
gery is indicated *early* when it appears that bleeding will not stop.
oint has been maintained by the advocates of the routine use of

surgical therapy for "massive hemorrhage." Statistics bearing on this point are presented in Table 161. Of 155 patients operated upon within 48 to 72 hours, 7.8 per cent died, but of 116 cases operated upon later, 39.7 per cent died. The difference is significant, but the average age is not available. Gordon-Taylor (22, 421) has expressed the opinion that the liberal use of blood transfusions will render late operations safer. Though this is likely, it seems reasonable that delayed operations will probably always carry a higher mortality.

Table 160

MORTALITY RATES OF GRAVE BLEEDING FROM PEPTIC ULCER WITH MEDICAL AND SURGICAL THERAPY

Author	*Year*	*Criteria*	*Medical*		*Surgical*	
			No.	*Deaths*	*No.*	*Deaths*
Hoerr, Dunphy, and Gray (18, 420)	1948	Exsanguinating blood loss failing to respond to transfusion	8	6 (75.0%)	6	2 (33.3%
Stewart et al. (16)	1948	Massive hemorrhage severe enough to depress RBC to 2.5 mil. within 24 hr.	21	6 (28.6%)	33	5 (15.2%
Sullens, Steigmann, and Meyer (19)	1949	Bleeding continuing after 48 hr. of medical treatment	14	8 (57.1%)	15	5 (33.3%
Bok (20)	1944	Relapse of hemorrhage within 72 hr.	9	6 (75.0%)	11	0 (0.0%
Jones (14)*	1947	Brisk recurrences of bleeding in elderly patients with proved peptic ulcer	..	50%	7	1 (14.3%
Total			52	26 (50%)	65	12 (18.5%

* Not included in total.

The difference between 50 per cent and 18.5 per cent is significant.

Surgery is indicated when bleeding stops and then occurs again whil the patient is still in the hospital on strict management. Though this supported by some evidence (17, 20, 28, 59) (see p. 569), more evidenc is needed. An operation is indicated only if the patient's condition suitable for a gastric resection. This is because local attacks by ligatin vessels or by excision may fail to control the bleeding, and gastroente ostomy alone merely diverts the gastric contents from the bleeding vesse Such operations have met with mediocre success (23, 24, 25, 422).

study of the blood supply of the duodenum shows that it is difficult to stop bleeding by tying blood vessels (58).

Table 161

DIFFERENCE IN MORTALITY BETWEEN AN "EARLY" AND "LATE" OPERATION FOR BLEEDING PEPTIC ULCER

Author	*Year*	*Early Operation (Within 48–72 Hours)*			*Late Operation (After 48–72 Hours)*		
		No. Cases	*No. Died*	*Per Cent Died*	*No. Cases*	*No. Died*	*Per Cent Died*
Oliani (21)	1936	10	1	10.0	5	2	40.0
Gordon-Taylor (22, 421)	1945	17	1	5.5	11	5	45.5
Finsterer (23, 422)	1939	78	4	5.1	74	22	30.0
Heuer (24)	1946	21	2	9.5	10	7	70.0
Jones (14)	1947	4	1	25.0	3	0	0.0
Hoerr et al. (18, 420)	1948	5	1	20.0	4	2	50.0
Amendola (25)	1949	11	1	9.1	3	3	100.0
Allen (26)	1942	9	1	11.1	6	5	83.3
Total	..	155	12	7.8	116	46	39.7

The difference between 39.7 per cent and 7.8 per cent is significant.

CHRONIC RECURRENT HEMORRHAGE. It is uncertain whether the repeated recurrence of hemorrhage in patients who are not under strict management should be an indication for surgery. Studies (28) have shown that bleeding ulcer patients tend to have a recurrence with hemorrhage more frequently than those with nonbleeding ulcers, but the data in the literature indicate that the first and subsequent hemorrhages are approximately equally dangerous; that is, the fourth hemorrhage is no more likely to be fatal than the first.

So, the important question is whether a patient who has bled is any more likely to bleed again after medical management than after surgical. Emery and Monroe (60) had 202 patients treated medically and then observed for an average of 3.6 years; of these, 19.3 per cent had bled before and after treatment. Of 155 patients treated surgically, chiefly by gastroenterostomy, and then observed for an average of 4.8 years, 17.4 per cent had bled before and after treatment. They point out that this difference is not significant. They state, however, that it is known clinically that some patients who bleed frequently after medical management stop bleeding after surgery. This statement is decidedly supported by the observations of Wilkinson and Tracey (29). They found that 74 per cent of 73 patients with multiple hemorrhages bled again after medical treat-

ment and only 33 per cent of 45 patients bled again after surgical t
ment during an average follow-up period of 4.3 years. Holdsworth (27) f
that 53 per cent of 134 patients hospitalized for bleeding ulcer and tr
medically bled again, whereas only 14.7 per cent of 68 patients tr
surgically bled again during a follow-up period of five years or more

Gastroenterostomy after several years of follow-up failed to pr
from recurrent hemorrhage in 22.8 per cent of 369 bleeding ulcer
followed for five years or longer after the operation (27, 30, 38, 39,
The same is true of the Devine operation (p. 982) for bleeding ulcer,
21 of 52 patients followed from four to nineteen years bled from an an
stomic ulcer (40). However, it appears from the evidence in Tabl
(Chapter 16) that the recurrence of bleeding is more common wh
gastroenterostomy is done for a bleeding than a nonbleeding ulcer.

Subtotal Gastric Resection. This does not provide complete
surance against the recurrence of a bleeding peptic ulcer, though
literature on the subject is rather meager. Wilkinson and Tracey (
the Lahey Clinic reported that 24 per cent of 41 patients treated by
tion for a bleeding ulcer bled again when followed for approximately
years. Of 173 patients treated by resection for duodenal ulcer at the
clinic, 6.8 per cent developed anastomotic ulcer and an additional 4
cent bled when followed (41). This again indicates that persons
develop bleeding ulcers maintain a tendency to bleed. Walters and C
land (45) of the Mayo Clinic treated 112 patients for bleeding p
ulcer by surgery and followed them for from four to eight years. Ble
occurred in 11.6 per cent, or 13 of the 15 (13.4 per cent) unsatisfa
cases. (In five of the 15, either the pyloric antrum had been left in
or an enteroenterostomy had been done.) Church and Hinton (4
lowed 44 patients resected for bleeding ulcer for a minimum of one
and an average of approximately four years, two, or 4.5 per cent,
again and none of 60 cases without preoperative bleeding bled. H
(27) followed 53 patients resected for bleeding ulcer for a minimum p
of five years and only two, or 3.8 per cent, had a recurrence of hemorr
(An additional 9.4 per cent had a recurrence of pain.) Thus, 27, or 10
cent, of 250 patients submitted to gastric resection for hemorrhage su
from a recurrence of hemorrhage in an average of four or more year

Summarizing, at least 25 per cent of peptic ulcer patients bleed s
festly during their life and 33 per cent of those admitted to a hospit
bleeding have bled before. Of those who have bled two or more t
55 to 75 per cent will have a recurrence of bleeding after medical ma
ment, 23 per cent after elective gastroenterostomy, and 11 per cent
subtotal resection. The mortality of medical management of ma
hemorrhage when it occurs actually is approximately 5 per cent
mortality of subtotal resection in patients properly managed medicall

tively should not be more than 1 to 2 per cent. Thus, subtotal gastric ion is indicated in patients who are subject to frequent or multiple rences of bleeding if the physician and patient choose to take the what greater risk of the operation in exchange for the hospitalization ated to the medical management of a recurrence. The concomitance ractable pain or obstruction with manifest hemorrhage enhances the ion for subtotal gastric resection.

LECTIVE SURGERY IN CONVALESCENT PERIOD AFTER ACUTE MASSIVE RRHAGE. In patients who have recovered from a massive hemor-, resection can be performed with a mortality of approximately cent, which is comparable with other elective subtotal gastrectomies 7). The aim of resection in the convalescent period is to prevent a rence.

The selection of cases should be guided by the age of the patient, the ber of previous hemorrhages, and the concurrence of other complica- such as pain or obstruction. With advancing age, the risk of hemor- increases. For that reason, Allen (46) has written that in a young n who has had a "massive" hemorrhage he advises a gastric resec- but in an older patient (above 45 years) he urges a resection in the alescent period. But, as indicated above, the patient who has had one hemorrhage may be carried on a medical regimen with less risk d if he has had two or more hemorrhages. Finally, intractable pain or ic obstruction frequently coexist with hemorrhage (7, 22, 46, 421). , the indications for an elective resection are multiple.

PERFORATION

cute perforation is widely considered to be a direct and immediate cation for surgery.

The discovery that some ulcers perforate enough to permit the entrance and some gastric or duodenal contents into the peritoneal cavity will spontaneously close with a subsidence of symptoms in six or eight (p. 553) has led some to believe that surgery may not always be ated in acute perforation. Since the aim of the treatment of perfora- is to stop leakage and to treat the peritonitis, it may be argued that ge may be stopped with continuous gastric suction and the peri- treated with antibiotics and sulfa drugs. This question will be dered in the last section of this chapter, along with the surgical ment of perforation.

INTRACTABLE PAIN

cute perforation, high-grade pyloric stenosis, and acute massive rrhage are operative indications because they represent a threat to et intractable pain is a *symptomatic* indication for surgical intervention.

The intractable pain may represent continuous or incapacitating pain which is unrelieved or only slightly relieved by strict medical management, or which recurs with even mild liberalization of the regimen. Or the intractable pain may represent frequent and severe recurrences which will respond, in part at least, to medical management, but the patient is unwilling or unable to comply with the medical management. Thus, surgical therapy may be indicated in an acute exacerbation which is unrelieved by medical therapy or by the inability to prevent frequent and severe recurrences.

The persistence of symptoms is frequently the result of penetration of the ulcer into an adjacent viscus. This is particularly true of duodenal ulcer where a posterior wall ulcer has penetrated into the pancreas. Anterior wall duodenal ulcers occurring alone are only rarely the cause of intractable pain requiring surgery (11, 48). Radiologic evidence of penetration is not in itself an indication for surgery. *The response to medical management* is the criterion for surgery (11).

Persistent indigestion is not to be considered intractable pain in a patient who follows self imposed or professionally prescribed mild restriction of the diet and irregular medication for distress. Surgery for intractable pain should be reserved for patients who have been subjected to strict medical management. We agree with Hinton and Maier (47), who recommend that if Sippy therapy does not cause abatement of symptoms, other medical procedures must be tried before the patients are termed medical failures. Every internist has observed that a change in regimen may be followed by relief and healing. Intractable pain has been the most common indication for surgery, which largely explains the difference in the percentage of ulcer patients referred to surgery by various internists. The range of the percentages referred to surgery for pain alone is 8 (7), 20 (42), 40 (12), 46 (43), and 56 (44).

Gastric Ulcer Suspected to Be Carcinoma

A greater percentage of gastric ulcers than duodenal ulcers are treated by operation because of the possibility of malignant degeneration of a benign gastric ulcer and the difficulty in differentiating between benign and malignant gastric ulcer.

The experimental, clinical, and histologic evidence of malignant degeneration of a benign ulcer has been examined in Chapter 21. It was concluded that the development of cancer from a benign gastric ulcer is infrequent, and that if a gastric ulcer is found to be malignant it probably was malignant at its inception. The danger of malignant transformation of a benign gastric ulcer is not an indication *per se* for surgical intervention.

On the other hand, great difficulty is sometimes encountered in dif-

ferentiating between benign and malignant gastric ulcers. There are some who believe that differentiation by clinical methods is so unreliable that all patients with gastric ulcer should be submitted to gastric resection. Others feel that efforts should be made to distinguish between those ulcers which can be trusted to be benign and those which must be suspected of malignancy.

Two arguments (Chapter 21) are presented by those who believe that gastric ulcer should always be treated surgically unless the individual's physical condition makes this inadvisable. *First*, if the surgeon or pathologist cannot make the diagnosis with certainty when he has the stomach open and can see and feel the lesion, how can anyone attempt to make a reliable diagnosis with any instrument short of the microscope? It was pointed out that this argument does not follow from the facts, since other methods of differentiation may be more reliable than examination of the gross specimen. The *second* argument is that the penalty of temporizing with malignant ulcers is greater than that of operating upon benign gastric ulcers. Sufficient data have not been published to either affirm or deny this contention.

The premises of the second argument are that 12 or 13 per cent (Table 118) of gastric ulcers, apparently benign, are malignant and that there are no known methods which can accurately separate benign and malignant lesions. Most malignant ulcers are resectable and these patients have an excellent chance of cure from their carcinoma. The surgical mortality rate of partial gastrectomy for gastric ulcer has been reduced to about 2 or 3 per cent in good hands (p. 997). Furthermore, gastric resection is excellent treatment for gastric ulcer, since postoperative recurrences are relatively rare and a high percentage of patients have satisfactory results (p. 1015).

There is no doubt that the five year survival of patients with all forms of gastric carcinoma is increased by an increased rate of resectability. Livingston and Pack (49), in analyzing the world's literature on carcinoma of the stomach to 1939, found that the average five year survival rate of all patients with gastric cancer was less than 2 per cent. Only about 25 per cent had resectable lesions. When State, Moore, and Wangensteen (50) had increased their resectability rate to 44 per cent in the 1936 to 1941 period, they had a five year survival rate of 6.7 per cent. Welch and Allen (51) had a 7 per cent five year survival rate during the 1937 to 1941 period when the rate of resectability was 50 per cent.

Malignant ulcers diagnosed preoperatively as benign have a much higher rate of resectability. Smith and Jordan (52) found that 75 per cent of malignant ulcers were resectable and Finsterer (53) was apparently able to resect almost all cancers with a preoperative diagnosis of be-

malignancy. On this basis, one would expect the five year survival rate to be markedly increased.

In addition, *there is some evidence that the five year survival rate of resectable malignant ulcers is greater than the five year survival rate of resectable gastric carcinomas as a whole.* Livingston and Pack (49), in a review of the literature, found that about 20 per cent of all patients with carcinoma of the stomach who survive resection are alive for five years. State et al. (50) found this figure to be 21.5 per cent, and Pack and McNeer (54), 34.7 per cent. However, Allen and Welch (55) found a five year survival rate of 4 per cent and Finsterer (55) found a five year survival rate of 35.5 per cent for gastric cancers thought to be benign preoperatively.

In summary, it appears that 75 per cent or more of gastric carcinomas masquerading as benign lesions are resectable and that 35 to 40 per cent of those with resectable lesions survive five years. Then, the five year survival rate of all malignant ulcers with a preoperative diagnosis of benignancy is 30 per cent or more. This is compared with a five year survival rate of 2 to 7 per cent for all carcinomas of the stomach.

Many gastroenterologists and surgeons are opposed to routine subtotal gastric resection for gastric ulcer. They believe that the diagnostic methods are accurate enough to determine those gastric ulcers which can be treated to be benign. They believe youth, high acid, a lesion on the lesser curvature less than 2.5 cm. in diameter, a roentgenologic and gastroscopic opinion of benignancy, and a favorable immediate response to medical management furnish enough circumstantial evidence to warrant the trust that the ulcer is benign. The accuracy and pitfalls of these methods have been presented in Chapter 21.

The most popular procedure has been the differentiation of benign and malignant ulcers by the therapeutic test. Benignancy is said to be indicated by a response to strict hospital management with complete subsidence of symptoms, complete disappearance of occult blood from the stool, and disappearance or marked healing of the crater in two or three weeks. Objection has been raised to the therapeutic test because malignant ulcers may become asymptomatic and actually appear to heal under the same regimen. Marshall and Welch (56) noted that nine of 26 patients under a medical regimen manifested symptomatic improvement with roentgenologic decrease in the size of the crater of the ulcer in spite of the fact that the ulcer was malignant.

Some indications of the accuracy of the diagnosis of benignancy are given by the reported incidences of gastric carcinoma in carefully diagnosed and medically treated cases. In Table 118, 651 cases of gastric ulcer managed medically have been collected. Forty-two, or 6.5 per cent, were eventually shown to have carcinoma. While this is considerably

cases which were suspicious enough to treat surgically, it nevertheless ates that the accuracy of diagnosis leaves something to be desired. chance of 6.5 per cent of carefully diagnosed gastric ulcers being gnant and the incident morbidity of a benign gastric ulcer must be ed against the 5 per cent mortality and 5 per cent morbidity of c resection for gastric ulcer.

nith and Jordan (52) have pointed out the frequency of carcinoma ients who have an early recurrence after medical therapy. About 15 ent of 82 patients who suffered from a recurrence were subsequently n by operation to have a carcinoma.

deally, gastric ulcers which are benign and uncomplicated should be ed by conservative measures, and surgery should be reserved for gnant ulcers and complicated benign ulcers. But, with the uncertainty ferential diagnosis, frequent surgical therapy can be neither con- ed nor supported; a continued search must be made for criteria will more accurately diagnose a gastric ulcer as benign or malignant.

Principles of Surgical Therapy of Peptic Ulcer, Excluding Its Complications

he important principles of surgical therapy are (a) to reduce acidity uch as is surgically and physiologically advisable, (b) to make the of the jejunum as short as possible, and (c) to avoid gastroenterostomy and enteroenterostomy. Other points have been considered in the and some of them may still have merit, namely, to rest the ulcerated by diversion of acid chyme, to relieve stasis, and to improve gastric ation.

Reduction of Gastric Acidity

he reduction of gastric acidity is an aim of both medical and surgical py. Although healing occurs in the presence of free acidity in the ch, "chronic" ulceration does not recur unless the stomach or its ant retain the ability to secrete hydrochloric acid. To prevent ent ulceration, the goal should be complete achlorhydria, rather he mere reduction of free hydrochloric acid. Although postoperative do not occur in the presence of a histamine-refractory achlorhydria, sult may be unsatisfactory because of postprandial distress, anemia, urbances of gastrointestinal motility.

should be emphasized again that evaluation of the effect of surgical dures on gastric acidity in man must be done carefully. The im- ce and difficulty of the proper placement of a stomach tube in the erative stomach should not be forgotten (31-33). The type of ant of gastric secretion used, the method of gastric analysis, the

presence or absence of bile in the samples, and a lack of a uniform
of reporting the results render a comparison of the results in the li
unsatisfactory and equivocal. Palmer and Norton (36) report that
analyses may be necessary to determine the actual presence of a fast
refractory achlorhydria; this we can confirm. In addition, the ea
late postoperative gastric acidities are not necessarily the sam
example, Lindsay and Evans (34) found that the early postop
achlorhydria after gastroenterostomy did not persist in 58 per
patients. Klein et al. (32) observed that the incidence of postop
achlorhydria after gastric resection for a gastric ulcer tends to i
with time. A similar result was observed when the resection was d
duodenal ulcer. Immediately after the operation, 38 per cent of
tients showed no free acid. When 108 of the 197 were tested from
eight years after resection, 56 per cent remained or had become
hydric, and 9 per cent showed a return of free acid where there ha
none before. The observations of Auguste and Paris (35) are confir
since the early postresection achlorhydria for gastric and duoden
increased from 72.7 and 36.8 per cent respectively to 93.7 and 74
respectively. Brunsgaard (71) also presents evidence that the inci
achlorhydria after gastric resection tends to increase with time
work should be done on this question because dogs after subtotal
resection show a gradual return of gastric acidity rather than a
for achlorhydria to occur with time.

Surgical procedures may reduce gastric acidity (1) by reduc
capacity of the glands to secrete acid, or (2) by decreasing the stim
of gastric secretion.

Reduction of Secretory Capacity of Gastric Glands. The
of the gastric glands to secrete acid may be reduced (a) by resectio
parietal cell area or (b) by reducing the blood supply to the gastric

Removal of Parietal Cell Area. This can be completely accom
only by total gastrectomy. It may be partially accomplished either
operation called fundusectomy or by the operation called subtota
resection. Subtotal gastric resection is designed to remove the
portion of the stomach and a major portion of the corporic or pari
area of the stomach. Fundusectomy removes a major portion of the
cell area without removing the pyloric portion.

Total Gastrectomy. An ulcer of the duodenum or jejunum ha
been seen in a patient or animal which has been subjected to
gastrectomy. It is now generally maintained that the surgical ri
high and the disturbances of digestion and absorption too fre
warrant the use of this operation for the treatment of peptic ulce

...undusectomy. Fundusectomy (Fig. 134, *11*) removes a wedge-shaped ...on of the corpus of the stomach, or the parietal cell area, with the ... of the wedge at the lesser curvature midway between the incisura ...cardia. It was introduced by Connell (37) in 1933 and has been ...ssfully employed in the prevention of experimentally produced post-...ive jejunal ulcer (93) (p. 338). It was introduced with the idea that ...icks the parietal cell area only and that removal of the pyloric portion ...e stomach is unnecessary. But as will be indicated later, considerable ...ence exists in support of the idea that the removal of the pars pylorica ...be important. Tubular resections and sleeve resections without a ...ejunostomy are similar to fundusectomy.

...However, fundusectomy does reduce gastric acidity for a period, after ...h it tends to return toward normal, depending on the extent of the ...trophy and regeneration of the gastric remnant (95).

...rtial Gastrectomy. Partial or subtotal gastric resection (Fig. 134, *9, 10,* ...) must be quite extensive in order to produce a significant decrease ...cretory capacity. In the dog, such an operation only decreases the ...ic phase of gastric secretion from 30 to 40 per cent.

...btotal Gastrectomy. In this, from one half to three fourths of the ...ach is removed, which results in anacidity in approximately 94 per ...nt of cases (247 out of 263 cases) of *gastric ulcer* (32, 64, 69, 71, 73) when ...e a test-meal or histamine is used as a stimulus. When from one half ...ree fourths of the stomach is removed for *duodenal ulcer*, approximately ...r cent of cases (683 out of 904 cases) (Table 162) have an anacidity ...est-meal or histamine (32, 41, 64, 66, 67, 69-73). This is undoubtedly ...e to the fact that the stomach of patients with duodenal ulcer secretes ...acid, on the average, than that of patients with gastric ulcer.

...studies have been made to ascertain whether the incidence of post-...ative anacidity is related to the amount of stomach removed. Such ...relation should obviously exist were it not for the fact that the gastric ...ant hypertrophies or regenerates to a variable extent. The data in ...erature fail to show a significant correlation (64, 73, 74). Nevertheless, ...Gaviser (73) reports that 82 per cent of 109 duodenal ulcer patients ...removal of three fourths of the stomach did not secrete acid when ...ed on repeated occasions with histamine. This is an impressive result. ...he cause of the achlorhydria which so frequently results after a three ...ch resection is not readily apparent, since mucosa which contains ...al cells is known to remain. Several factors may be concerned: (1) ...parietal cells in the fundus may not be as readily stimulated by hista-...as those in the corpus (81, 82). (2) The operation may devascularize ...remnant (86). (3) A gastritis may occur. The latter suggestion has the

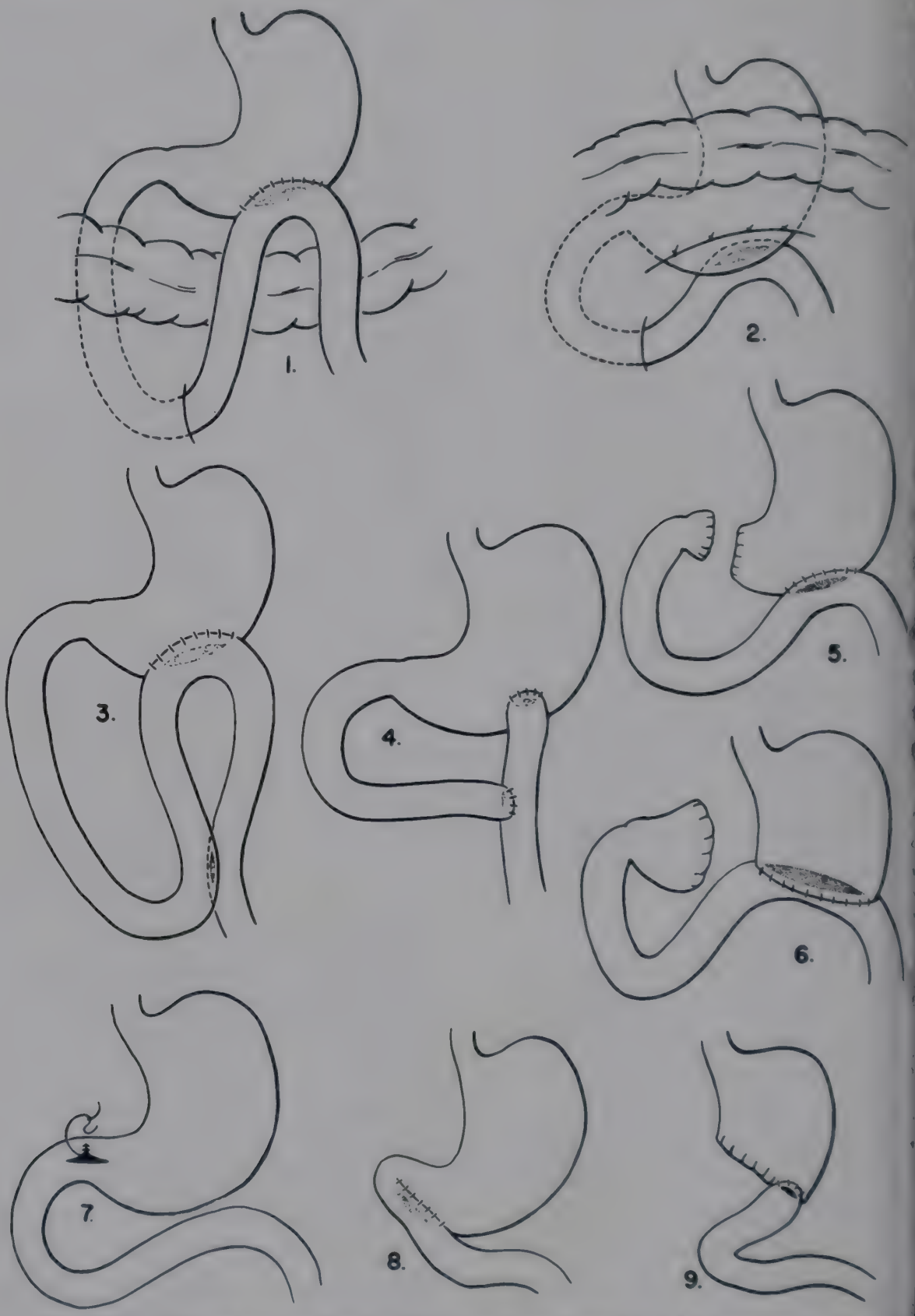


FIG. 134. Various operations which have been used for the treatment of pept ulcer:

1. Anterior gastrojejunostomy (gastroenterostomy).
2. Posterior gastrojejunostomy (gastroenterostomy).
3. Gastroenterostomy with (Braun's) enteroenterostomy.
4. Gastroenterostomy with Roux-en-Y anastomosis.
5. Gastroenterostomy with pyloric exclusion (von Eiselsberg).
6. Devine's pyloric exclusion operation (no stomach is resected).
7. Heineke-Mikulicz pyloroplasty.

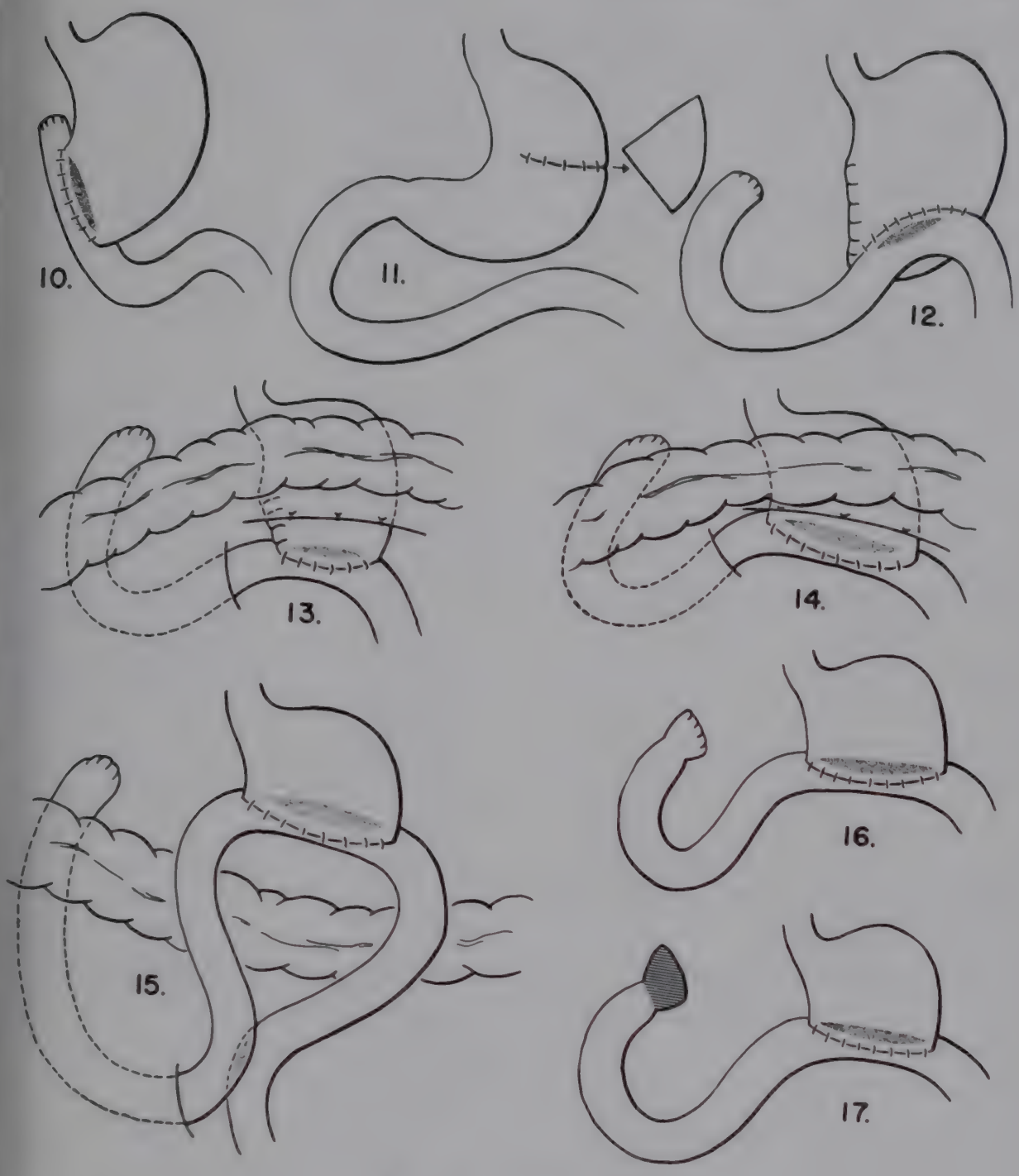


FIG. 134 (*Continued*).

8. Finney pyloroplasty (gastroduodenostomy).
9. Billroth I gastric resection.
10. Finney-Haberer modification of Billroth I gastric resection.
11. Connell's fundusectomy.
12. Billroth II gastric resection.
13. Hofmeister modification of Billroth II gastric resection (posterior or retrocolic anastomosis).
14. Pólya modification of Billroth II gastric resection (posterior or retrocolic anastomosis).
15. Pólya type gastric resection with anterior (antecolic) anastomosis and entero-enterostomy.
16. Finsterer's resection with pyloric exclusion (the remnant of the pars pylorica is not resected).
17. Finsterer's resection with pyloric exclusion and excision of the pyloric mucosa (the mucous membrane of the excluded pyloric remnant is excised).

Table 162

EFFECT OF GASTRIC RESECTION ON GASTRIC ACIDITY

Author and Year	*Type of Test*	*No. of Cases*	*Results* — *Units Free Acid*				*Comment*
			0	*1–20*	*21–60*	*61+*	
		Gastric Ulcer					
Klein et al. (1933) (32)	Test-meal and histamine	38	36	2	0	0	
Bruusgaard (1948) (71)	Caffeine test-meal	140	137	3	0	0	
Holman et al. (1943) (64)	Histamine	12	9	0	3	0	½ to ⅔ resected
Gaviser (1947) (73)	Triple histamine	50	44	4	2	0	Triple histamine, ¾ resected
Watson (1947) (69)	Test-meal	23	21	2	0	0	⅔+ resected
Total	..	263	247	11	5	0	94 per cent anacid
		Duodenal Ulcer					
Klein et al. (1933) (32)	Test-meal and histamine	108	61	..	..	..	No recurrences in 61 cases remaining anacid; nine in 47 cases secreting acid; 40 per cent of 61 histamine-anacid
Perman (1936) (66)	Test-meal	48	31	13	4	0	Tested two weeks to five months postoperative
St. John et al. (1939) (67)	Test-meal	26	22	2	2	0	
Kiefer (1942) (41)	Test-meal	141	96	..	..	..	70 per cent of 23 with anacid to test-meal were anacid to histamine; 12 recurrences, all with free acidity above 20
Watson (1947) (69)	Test-meal	25	20	5	0	0	⅔+ resected
Friberg (1946) (70)	Not given	105	94	6	5	0	
Bruusgaard (1948) (71)	Caffeine test-meal	140	129	3	8	0	
Holman et al. (1943) (64)	Histamine	34	16	9	9	0	½ to ⅔ resected; all anastomotic ulcer had 60+ units free acidity
	Histamine	4	1	2	1	0	⅔+ resected
Friedell (1941) (72)	Fasting	43	32	—	—	—	½ resected
		65	50	—	—	—	½+ resected
Gaviser (1947) (73)	Triple histamine	109	90	8	13	0	¾ resected
Bartels (1947) (74)	Histamine	26	18	—	—	—	¾+ resected; anacid in 70 per cent
		30	23	—	—	—	⅔ resected; anacid in 77 per cent
Total	..	904	683	—	—	—	76 per cent anacid
Total, including only those giving complete data	..	491	403	48	42	0	82 per cent anacid
Watson (1947) (69)	Histamine	22	8	8	6	0	Resection for exclusion with mucosal excision
Gaviser (1948) (73)	Triple histamine	30	26	3	1	0	Resection for exclusion with mucosal excision
Total	..	52	34	11	7	0	65 per cent anacid
Lorenz et al. (1922) (65)	Test-meal	43	40	—	—	—	No recurrences; entire antrum removed
		12	11	—	—	—	Part of antrum left in and several recurrences suspected in the 12 patients

most evidence in its support, since a high incidence of gastritis has been reported to have been found on gastroscopic examination (84, 85). The cause of this gastritis, unless due to partial devascularization, is uncertain.

Ligation of Gastric Arteries or Blood Vessels. This has been done in human patients with peptic ulcer and in dogs with the idea that the decrease in blood supply would decrease the secretion of gastric juice.

In dogs, complete ligation of the blood vessels except those which supply the cardiac and pyloric sphincter is reported to cause gangrene of the stomach (90, 91). This has not been true in our hands if great care not to traumatize the stomach is exercised. Dissecting out and tying all the veins sometimes causes death, regardless of the exercise of care. All the arteries may be ligated without causing any necrosis, though some (91, 92, 94) have reported that ulcers developed on the greater curvature. When all the arteries, or veins, or blood vessels are ligated, a marked decrease in the volume of secretion occurs (94); this does not occur if only a few large arteries are ligated (90–92). When all the vessels are ligated, the anacidity is only temporary. When the major portion are ligated, the secretion returns to normal in a few months (95). We (95) ligated the major portion of the blood vessels to the stomach and found that it prevented the development of ulcers in only three of 11 Mann-Williamson dogs, because in time the secretion of acid returned to normal. Holm and MacKay (96), using Mann-Williamson dogs, observed no protection against postoperative ulcers. LeVeen (94) observed protection and Baronofsky (97) did not observe protection against histamine in beeswax ulcers. This lack of agreement is not surprising in view of several factors, such as differences in surgical technic, differences in diet, and differences in the susceptibility of different dogs, which affect the time of onset and incidence of ulcer in such experiments. Opinion also differs regarding the permanency of the effect of devascularization (91, 94).

Ligation of the gastric arteries has been employed extensively by Hey (89) and Somervell (88). Hey divides or quadruply ties, to prevent regeneration of the sympathetic nerves, all the blood vessels on both curvatures from the esophagus to 2.5 cm. proximal to the pyloric sphincter. A gastroenterostomy is performed to provide against stenosis on healing of the ulcer. He has indicated that the acidity is reduced for about nine months. Somervell (88) ligates all the vessels on the lesser curvature and five or six branches of the gastroepiploics on the greater curvature. In fourteen patients followed from one to five years, the average fasting free acid was reduced from an average of 80 C.U. preoperatively to 40 C.U. postoperatively. Similar results were obtained in 94 patients in whom gastroenterostomy was performed in addition to the ligation of the principal arteries of the stomach. These results indicate that a relatively

permanent reduction of acid output occurs in man after ligation of the major arterial supply of the stomach; however, Wood (119) has recently reported on the late effects (1.5 to four years) of the Somervell operation on the gastric acidity of 17 patients, finding that the acidity had returned practically to the preoperative level.

Reduction of Stimulation of Parietal Cells. Surgical procedures which have been employed with the idea of reducing the stimulation of the parietal cells are: (1) resection of the pyloric antrum, (2) pyloroplasty and gastroenterostomy to facilitate gastric emptying, and (3) partial or total vagotomy.

Much of the literature dealing with this subject is confusing because it has been based on erroneous conceptions of the physiology of gastric secretion and on fallacious reasoning. It might be pointed out here that the failure of the elimination of some stimulus for gastric secretion to cure peptic ulcer does not signify that the stimulus has no importance in normal physiologic processes. Conversely, the fact that the elimination of one of the mechanisms for gastric secretion leads to healing of the ulcer does not prove that this mechanism was primarily disordered and was the cause of the ulcer. It should be recalled that the mechanism for the increased secretion in most duodenal ulcer patients has not been definitely established.

Removal of Pars Pylorica: Pylorectomy. Though the pyloric portion of the stomach does not secrete acid as some surgical articles suggest, the mucosa of this portion of the stomach does form the gastric hormone gastrin. However, nothing is really known about the role this hormone may play in the genesis of the hypersecretion of acid in duodenal ulcer, and it certainly does not have any influence in determining the variations in the susceptibility of the jejunal mucosa to acid chyme. Hence, it is not surprising that an anastomotic ulcer occurs in some patients after the removal of the pyloric portion of the stomach. There can be no doubt that pylorectomy decreases to some extent the total secretion of acid, but there are some patients in whom the reduction is not enough to prevent their susceptible jejunal mucosa from being injured.

The failure of pylorectomy to prevent the formation of an anastomotic ulcer does not argue against the formation of gastrin by the pyloric mucosa. Neither does the fact that pylorectomy prevents recurrences in some patients prove that gastrin was the cause of the ulcer. This latter statement is true because pylorectomy also facilitates enterogastric regurgitation and gastric evacuation and decreases the motor drive of gastric peristalsis by replacing the pyloric orifice with a larger opening.

All investigators (98–104) except one (105) have observed a moderate to marked decrease in the secretion of acid after pylorectomy in dogs. Those who have studied the late as well as the early effects of the operation

on the acidity of the gastric contents have found a return to preoperative values in several weeks to several months.

In man, pylorectomy rarely produces a histamine-refractory achlorhydria (9, 10), but Lorenz and Schur (65) found anacidity after a test-meal in 40 of 43 patients after pylorectomy. However, in some of the patients, as much as half of the stomach was resected, and it is not stated whether the test-meals were performed immediately after operation or at some time later. This is an important consideration, since in dogs gastric acidity returns to normal a few months after pylorectomy.

Another practical consideration arises regarding the role the pyloric portion of the stomach plays in gastric secretion. Finsterer (106) introduced the operation of subtotal gastric resection with pyloric exclusion (Fig. 134, *16*), in which the distal part of the pyloric portion of the stomach is not excised but closed with sutures, because the tissues about the duodenal ulcer are so inflamed or adherent that transection and closure of the duodenum would be dangerous. Gastrointestinal continuity is reëstablished by a gastrojejunostomy. In such cases, the incidence of postoperative anastomotic ulcer has been unusually high, more than 20 per cent (p. 1020), unless the mucosa of the portion of the pars pylorica left behind is excised (Fig. 134, *17*).

The relation of excising or not excising the mucosa of the pyloric remnant to gastric acidity is not clear. One group of investigators (63, 73) has found that only 25 per cent of patients developed histamine-refractory achlorhydria when the mucosa was left in, as compared to 80 per cent when the mucosa was excised. Another investigator (69), however, found that only 37 per cent of 22 patients developed achlorhydria to a test-meal after pyloric exclusion when the mucosa was excised. Resection of the pyloric remnant has apparently cured the recurrences in 29 patients who developed an anastomotic ulcer after a subtotal resection with pyloric exclusion (p. 1024). Unfortunately, pre- and postoperative gastric acidity values have not been published for patients with anastomotic ulcer cured by resection of the excluded pars pylorica.

How the pars pylorica acts to prevent a reduction in gastric acidity or favors the formation of an anastomotic ulcer, since its mucosa is excluded from the stream of gastric contents, is not clear. Instead of seeking the answer to this question, one might suggest that those patients in whom the pars pylorica must be excluded are severe cases of peptic ulcer and are more susceptible to a recurrence. For this reason, the incidence of anastomotic ulcer might be higher in them than in the average patient who is submitted to a gastric resection. If this were true, the incidence of anastomotic ulcer would not be decreased a statistically significant extent by excision of the mucosa or of the pyloric remnant after an anastomotic

ulcer has occurred. However, the incidence is decreased by a statistically significant extent and we must seek an explanation other than the type of patient subjected to the operation. Since so many subtotally gastrectomized patients develop a gastritis along with achlorhydria, is it possible that the presence of the pyloric mucosa in the body prevents gastritis? A more acceptable hypothesis is that in the presence of the pyloric mucosa some gastrin is being produced and stimulating the secretion of acid, even though the mucosa is not bathed with gastric contents. Or, it is possible that pancreatic juice and bile regurgitate into the lumen of the pyloric remnant and stimulate the production of gastrin.

Reduction of Gastric Emptying Time. The duration of the gastric phase of gastric secretion depends upon the length of time the food remains in the stomach. Less gastric juice should be formed if gastric evacuation is facilitated. It is also possible that too rapid emptying of the stomach excites reflexes which inhibit gastric secretion. On the other hand, irritation of the intestinal mucosa may release histamine, which would stimulate gastric secretion, or the intestinal phase of gastric secretion might be unduly prolonged. Also, a prolonged intestinal phase in a stomach that contained no food would expose the intestinal mucosa to considerable unbuffered acid.

These factors are considered because, after gastroenterostomy, pyloroplasty, or gastric resection, emptying of the stomach is usually faster than in the normal stomach. Although motor activity plays a major role in gastric evacuation, mechanical factors affect gastric evacuation through an artificial stoma. Bruusgaard (71) has observed that if the stoma of a simple gastroenterostomy be placed at a site higher than the most dependent part of the stomach, emptying is rapid until the level of the stomach is reached.

Vagotomy. Vagotomy may favorably affect peptic ulcer as a result of changes in gastric secretion and motility.

Though gastric secretion is not significantly influenced by the section of one vagus (121, 122), the cephalic phase of gastric secretion is completely abolished by complete vagotomy. Hypersecretion hypothetically due to an "anxiety or tension state" should also be abolished. In addition, all the phases and mechanisms for the stimulation of gastric secretion are depressed, including the response to histamine (125–127, 130). Nocturnal secretion in peptic ulcer patients has been found to be decreased approximately 50 per cent in volume by all observers (123–125). The results of Stein and Meyer (125), obtained soon after operation, are shown in Table 163.

Gastric secretion in response to histamine or a test-meal returns approximately to normal six months or more after vagotomy in dogs (126,

128). Data warranting a similar statement for man are not available; however, some data indicate that the decreased acid and volume output during the night persists for at least two years (124, 129).

Table 163

TWELVE HOUR NIGHT SECRETION BEFORE AND AFTER VAGOTOMY*

	Free Acid Milliequivalents		*No. of Determinations*	*No. of Patients*
	Mean	*Range*		
Before operation	47.4	0–154.0	70	22
After operation, complete vagotomy with gastroenterostomy	1.5	0– 11.8	38	14
Complete vagotomy without gastroenterostomy	3.0	0– 12.3	13	4
Incomplete vagotomy	12.7	3.2– 48.5	10	3

* Stein and Meyer (125).

Section of the vagi also decreases "motility on tone" or type II and III contractions of the stomach. This would tend to decrease any mechanical factors secondary to spasm or hypertonus which may be contributory to the chronicity of an ulcer. These changes, however, favor gastric retention of solids, which always occurs after complete vagotomy (123, 133, 134, 234). Delayed emptying of the stomach tends to persist for at least nine months (124, 125). Though pyloric stenosis may be the cause of the delay in some instances, a decrease in tone or "strength of the peristaltic contractions" is the basic cause (123, 134).

There is no evidence in man showing that vagotomy has a favorable effect on the secretion of mucus by the stomach or Brunner's glands. The effect on blood flow is unknown, but if the vagus contains vasodilator nerves, then the vasoconstrictor action of the splanchnic fibers is unopposed after vagotomy.

The operation does not section nerves responsible for conducting pain impulses, since the introduction of acid (200 cc. of 0.1 N HCl) into the stomach of an ulcer patient a few days after complete vagotomy induces ulcer pain (132). Nor does the operation impair the sensations of gastric distension, nausea, or appetite (123, 131).

Although there is a tendency for return of gastric secretion to normal and return of tone to the gastric musculature, it has not been demonstrated that the secretory and motor fibers of the vagus nerves actually regenerate. No evidence of regeneration of the motor fibers in the dog has been obtained during a two year study.

Facilitation of Enterogastric Regurgitation. Simple gastroenterostomy, pyloroplasty, and gastric resection very probably facilitate enterogastric regurgitation. In fact, this is one of the reasons given in support of these operations. It was on the basis of such an opinion that Schmilinsky (135) performed a gastrojejunostomy with total intragastric regurgitation. Numerous experiments in dogs indicate that this procedure predisposes to ulcers in the efferent jejunal loop (35, 109, 136, 137). Its use in the treatment of peptic ulcer in man is surely unjustified, since it exposes the efferent jejunal loop to only slightly buffered gastric juice.

Similarly, cholecystogastrostomy has been performed in an attempt to buffer gastric juice (139). Clinically, 40 per cent of patients have had recurrence of symptoms within two years (107). Also, there is danger of ascending cholangitis with such a procedure (140).

The idea of neutralizing and diluting acid chyme at its source in the stomach appears to be sound on superficial examination. However, it must be recalled that bile and succus entericus are not very alkaline, though they can serve to buffer and dilute acid (110). Pancreatic juice is quite alkaline but when the stream of acid chyme is diverted away from the duodenum, the secretion of pancreatic juice is diminished. In experiments on dogs, it has been reported by Kesavalu and Mann (108) that the total drainage of the duodenal juices (pancreatic juice, bile, and duodenal juice) into the stomach in the presence of a gastrojejunostomy did not significantly decrease the gastric acidity. The failure of the gastric acidity to be decreased significantly may be due to the stimulating action of the duodenal juice on gastric secretion which has been reported to occur (108, 109).

Rest of Ulcerated Part by Diversion of Acid Chyme, Improvement of Emptying, and Relief of Stasis

Gastroenterostomy (Fig. 134, *1*, *2*) was first performed by Wölfer in 1881 to relieve high-grade pyloric stenosis due to cancer. It was not long until the operation was introduced for the treatment of duodenal and gastric ulcer. It is interesting to note that at least 32 modifications of the original operation have been proposed (1).

Gastroenterostomy has been used for the treatment of peptic ulcer for several alleged reasons. First, it diverts some of the acid chyme into the jejunum and gives some rest for the ulcerated area. Second, it improves gastric emptying by providing the stomach with two orifices, relieves any gastric stasis that might result from spasm or organic stricture, and tends to decrease the tension or pressure in the stomach. These factors are known to delay the healing of gastric ulcer. Third, it allows all the duodenal juices to enter the stomach to neutralize acid at its source. Fourth,

it has been suggested that gastroenterostomy takes "the strain off the muscle in the floor of the ulcer near the pylorus" (112). The proponents of this hypothesis believe that the operation is commonly followed by atrophy of the muscle in the pyloric ring (113, 114).

The favorable and unfavorable influences of these various factors have been discussed, with the exception of the diversion of acid chyme.

Diversion of Acid Chyme of Gastric Contents. It has been clearly demonstrated that the diversion of acid chyme so that it will not bathe an anastomotic ulcer results in the healing of the ulcer (p. 347). It is well known that after a well functioning, simple gastroenterostomy, a duodenal ulcer will heal, *to recur again if the stoma fails to function well* (111). Also, postoperative jejunal ulcer has been treated by disconnection of the gastroenterostomy so that all the chyme again traverses the duodenum, and the duodenal ulcer has recurred.

We believe that in view of this evidence the chief reasons why the gastroenterostomy is successful in many cases of duodenal ulcer are (a) that some of the acid chyme is diverted from that area so that the area can tolerate the amount that it does receive, and (b) that the acid chyme which is diverted into the jejunum is inadequate to overtax the tolerance of that area for acid.

This interpretation is most reasonable in view of the fact that anacidity persists longer than six months (Table 164) in not more than 20 per cent of gastroenterostomized ulcer patients, and in 60 per cent there is hyperacidity or normal acidity. The tolerance of the jejunum of some patients must be quite low, since some patients with achlorhydria in response to a test-meal develop jejunal ulcer; either this is so or some other factor than acid is involved in the causation of these ulcers (120).

A Short Jejunal Loop

The most desirable point of an anastomosis of the stomach to the intestine would be the upper end of the duodenum, after an ulcer, if present there, has been resected. This is usually inadvisable when a large gastric resection is done because of the presence of an adherent or inflamed duodenum or the anastomotic difficulty of mobilizing the duodenum.

The reasons why a high jejunal anastomosis is desirable are: (1) The more oralward mucosa is less susceptible to injury with acid chyme. (2) The gastrointestinal hormones (viz. enterogastrone, secretin, and cholecystokinin) are more abundant in the oralward mucosa. (3) The spatial separation of the point of entry of the gastric contents and the pancreatic juice, bile, and Brunner's secretion prevents a rapid regulation of intestinal acidity by the alkaline secretions. (4) It is probable that a significant fraction of the excess alkalinity or base of pancreatic juice is absorbed along

Table 164

EFFECT OF GASTROENTEROSTOMY ON GASTRIC ACIDITY

Author and Year	*Type of Test*	*No. of Cases*	*Results* — *Units Free Acid*				*Comment*
			0	*1–20*	*21–40*	*41+*	
	Reports Showing Decrease						
Cole et al. (1898)*	Test-meal	16	3	4	6	3	..
Hartman et al. (1899)*	Test-meal	6	1	2	0	3	..
Kramer (1906)*	Test-meal	34	7	5	12	10	..
Kreuzer (1906)*	Test-meal	26	0	12	11	3	..
Petren (1911)*	Test-meal	28	0	9	10	9	..
Nielsen (1919)*	Test-meal	38	8	30	0	0	..
Berberich (1920)*	Test-meal	35	15	4	16	0	..
Conybeare (1922) (75)	Test-meal	28	13	3	6	6	..
Wydler (1922)*	Test-meal	36	13	5	14	14	..
Hunter (1923)*	Test-meal	10	2	0	2	6	..
Ohly (1924)*	Test-meal	45	2	22	8	11	..
Devine (1925) (77)	Test-meal	19	9	2	4	4	..
Bruusgaard (1948) (71)	Caffeine	174	77	18	42	47	..
Lindsay et al. (1929) (34)	Test-meal	60	20	9	12	19	33 per cent anacid
Total	..	553	170	125	143	135	31 per cent anacid
Sherren (1924) (76)†	Test-meal	408	250	80	60	38	Early postoperative 5 per cent anacid
	Reports Showing Little Change						
Kausch (1899)*	Test-meal	6	0	0	3	3	..
Renckl (1901)*	Test-meal	14	0	2	8	4	..
Kindl (1909)*	Test-meal	5	0	1	2	2	..
Schur (1911)*	Test-meal	12	0	2	7	3	..
Troell (1911)*	Test-meal	9	1	0	7	1	..
Elman et al. (1935)*	Test-meal	7	0	1	4	2	..
Luff (1930) (79)	Test-meal	123	12	0	5	106	..
		176	13	6	36	121	7 per cent antacid
Lewisohn et al. (1925) (78)	Test-meal	11	0	1	2	8	Preoperative
		11	0	1	5	5	Postoperative gastroenterostomy
	Test-meal	46	0	2	14	27	Preoperative
		46	2	7	24	13	Postoperative gastroenterostomy with pylorus exclusion
Perman (1936 (66)	Test-meal	25	0	4	6	15	Postoperative gastroenterostomy with pylorus exclusion
Heuer et al. (1943) (80)	Histamine	50	0	0	5	45	Preoperative gastroenterostomy
		75	1	2	2	70	Postoperative gastroenterostomy
Wangensteen & Lannin (1942) (63)	Histamine	29	0				..

* Cited by Holman and Sandusky (31).

† Sherren's figures represent observations made the first few weeks postoperatively. Lindsay & Evans were made in the same hospital and show that the early results do not persist in 38 per cent of patients.

with some fluid during passage through a long afferent loop. (5) This would be increased by any tendency toward stasis in a long afferent loop. In any case, an attempt should be made to select the loop so that neither its length nor shortness will predispose to stasis.

Much evidence from the experimental laboratory emphasizes the importance of making the gastroenteric anastomosis as high in the jejunum as possible (115–117, 137, 141). We have gained the impression from the literature that those surgeons who have used the short loop have a lower incidence of anastomotic ulcer. This is not subject to clear proof and for that reason tabular material supporting the impression has been omitted here.

Avoidance of Gastroenterostomy En-Y and Enteroenterostomy

Before the intestinal gradient to injury by acid chyme was generally known, the operation of gastroenterostomy en-Y (Fig. 134, *4*) or with enteroenterostomy (Fig. 134, *3, 15*) was performed to insure against stasis in the afferent loop, whether it was made short or long. It was soon learned that these operations are to be avoided because they divert the alkaline juices away from the stoma of the gastroenterostomy and render the mucosa more vulnerable to acid injury. In fact, these operations produce an abnormal physiologic condition approximating the Mann-Williamson dog. Good drainage of the afferent loop is essential but it should not be attained by the use of unsound physiologic principles.

Removal of Ulcer-bearing Tissue

Simple excision of a peptic ulcer was designed to remove the disease by removing the ulcer. Recurrences occurred in the majority of cases because no attack was made on the factors responsible for the ulcer. This is eloquent proof that peptic ulcer is not merely a circumscribed local disease. When combined with gastroenterostomy or pyloroplasty, excision of the ulcer probably played an insignificant role when a satisfactory result was obtained.

It is very probably unnecessary for a duodenal ulcer to be resected during a gastrectomy. The results of partial gastrectomy with and without removal of the ulcer are similar, provided no pyloric mucosa is left. A duodenal ulcer will heal if protected from gastric secretion. (See p. 1019, Nonresectable Duodenal Ulcer.)

The principle of treating peptic ulcer solely by removing the area in which ulcers develop spontaneously is basically unsound. Unless other factors are altered, all that is accomplished is to shift the burden to an area less capable of resisting ulceration, namely, the jejunal mucosa. As with simple excision, when operations which remove the ulcer-bearing area

effect a cure, they do so by altering other factors to be discussed below. Gastrectomy may remove not only the ulcer but also the "ulcer-bearing region" of the stomach and duodenum. At the same time, it deals with certain causative factors. This is particularly true of gastric resection for gastric ulcer, where mechanical factors may play an important role in the etiology of the lesion. Recurrences are uncommon after partial or subtotal gastric resection for gastric ulcer (p. 1015). By contrast, ulcers do recur in the stomach after gastroenterostomy, even when the operation has been done for duodenal ulcer (p. 1005).

Comment

It is quite obvious that with the possible exception of fundusectomy, all of the operations for peptic ulcer involve the application of combinations of two or more of the principles listed and briefly discussed.

For example, the operations of subtotal gastric resection and simple gastroenterostomy are similar in some respects. *Gastric resection* (1) reduces the amount of acid and gastrin-secreting mucosa, (2) removes the gastric ulcer-bearing area, (3) diverts the acid chyme away from the ulcer in the duodenum, and (4) facilitates gastric emptying and enterogastric regurgitation. This operation, however, places all the remaining burden on the jejunal mucosa. *Gastroenterostomy partitions the burden between the duodenal and jejunal mucosa.* It does nothing toward decreasing the capacity of the stomach to secrete acid and decreases the stimuli for gastric secretion only through facilitating gastric evacuation.

Which is superior depends on the clinical results, which not only include the extent to which recurrences are prevented but also the mortality and the undesirable sequelae of the operations.

Immediate Mortality Rate of Elective Operations for Peptic Ulcer

Introduction

When considering the advisability of electing an operative management for peptic ulcer, the immediate mortality of the operation must be considered in relation to the mortality of peptic ulcer managed medically. Since the overall mortality of peptic ulcer is not more than 3 per cent, the mortality of the operative management must be low. In certain instances, such as repeated hemorrhage, where the anticipated mortality is 5 to 10 per cent, it must be remembered that the expectancy of a fatal outcome on medical management is greater than that of the average case of peptic ulcer. Of course, the risk of the patient developing a "dumping-stomach syndrome," or an anastomotic ulcer, which may manifest intractable pain,

hemorrhage, or perforation, or one of the less serious sequelae must be considered. However, the purpose of this section is to present only the immediate mortality rate of elective operations.

In presenting the immediate mortality rate of elective operations, we have excluded operations for malignant disease and for emergencies, such as hemorrhage and perforation, where the mortality rate is higher.

It should be indicated that the mortality rates reported in the literature are usually those of the larger clinics. They represent the results of experienced surgeons working with their resident staff over a period of time, during which the mortality rate is further reduced by the acquisition of specialized experience with the operation. This is particularly true of gastric resection but is undoubtedly true of operations of lesser magnitude. For example, Lahey and Marshall (218) have written: "There is no operation in which a relatively large experience and frequent practice is more important and more necessary than in that of subtotal gastrectomy if the mortality rate is to be reduced and kept low."

There is adequate evidence to support this statement. Lahey and Marshall reported a mortality of 18 per cent in their early resection cases and 11 per cent at a later date. More recently, Lahey (188) has reported a mortality rate of less than 2 per cent in approximately 700 resections for gastric, duodenal, and jejunal ulcers. Visick (86) reported a mortality of 12 per cent in his first 75 cases, but only 3.7 per cent in the last 430. Lake (184, 219) reported a mortality rate of 9.5 per cent in his first 242 cases but in the last 130 cases a mortality of a little over 3 per cent. St. John et al. (193) reported mortality rates of 20 per cent from 1926 to 1935, 4.6 per cent from 1936 to 1945, and 2.5 per cent for 1946 to 1947. Bartels and Dulin (74) reported mortality rates of 28 per cent from 1927 to 1940, 8 per cent from 1941 to 1943, and 1.6 per cent from 1944 to 1945.

In evaluating the mortality of various operations, it is necessary to consider the period in which the operations were performed. The advent of chemotherapy, antibiotics, fluid and vitamin therapy, improvements in anesthesia, easily available blood transfusions, and continuous gastric suction have made all operations safer. It is also important to take into account the selection of patients. If good risk patients are selected for gastric resection and poor risk patients for operations of lesser magnitude, the mortality rates of the two groups are not comparable.

Unfortunately, operative mortality has been reported differently by various authors. Some report only hospital deaths, and others properly report deaths which occur after release from the hospital when they can be traced directly to the operations, such as bowel obstruction, homologous serum jaundice, etc. Such deaths should be reported, though there may be a difference of opinion relative to their interpretation. The same holds

for deaths from pneumonia, pulmonary emboli, and other complications. It is entirely satisfactory to present those patients who died "only as a result of the operative procedure" and to figure a mortality due to technical failure only. However, the risk of the operation represents all deaths attributable directly or indirectly to the operation, and such data and such a mortality rate should also be presented and considered in relation to the risks of nonoperative management.

Mortality Rate of Pyloroplasty and Gastroenterostomy

Reports on the mortality rate of pyloroplasty (Table 165) and of gastroenterostomy (Table 166) have been assembled. The average mortality rate for pyloroplasty was found to be 2.5 per cent in 842 cases (range, 0.4 to 5.2 per cent). The average mortality rate for gastroenterostomy was found to be 3.8 per cent in 10,274 cases (range, 0.1 to 12.3 per cent).

Table 165

Mortality Rate of Pyloroplasty

Author	*Year*	*No. Cases*	*No. Died*	*Per Cent Died*
Horsley (143)	1930	78	3	3.8
Judd & Hazeltine (142)	1930	464	2	0.4
Finney & Hanrahan (144)	1930	251	13	5.2
Perman (66)	1936	25	2	4.0
St. John et al. (145)	1939	24	1	4.2

The mortality rate is higher in the earlier and smaller series, which suggests that the experience of the surgical team may have been involved. It would also appear that the mortality may be higher when gastroenterostomy is performed for gastric than for duodenal ulcer. The data, however, are contradictory, some finding the mortality rate for gastric ulcer higher (152, 168, 208), some lower (144), and some the same (157). In the case of pyloroplasty, Finney and Hanrahan (144) found the mortality to be higher when the operation was done for gastric than for duodenal ulcer. Since most of the differences are statistically significant, they must have been due to some other factor than the site of the ulcer, such as the selection of patients for the operation.

It should be emphasized that the mortality rates presented represent only approximations when applied to the present period. A mortality rate of 3.8 per cent for gastroenterostomy is probably too high for the average experienced surgeon of today. Nevertheless, gastroenterostomy

Table 166

MORTALITY RATE OF GASTROENTEROSTOMY

Author	*Year*	*No. Cases*	*No. Died*	*Per Cent Died*
von Eiselsberg (146)	1914	284	15	5.4
von Haberer (147)	1918	83	1	1.2
Nicolaysen (200)	1919	329	19	2.7
Pool & Dineen (148)	1922	70	6	8.6
Clairmont (161)	1924	448	27	5.4
Flörcken (162)	1924	164	6	3.8
Paterson (150)	1926	495	4	0.8
Tanaseco (149)	1928	118	7	6.8
Luff (79)	1929	1328	62	4.8
Finney & Hanrahan (144)	1930	260	21	8.1
Douglas (152)	1930	187	8	4.3
Horsley (143)	1930	57	7	12.3
Gatewood (163)	1930	264	7	2.6
Hoffmann (153)	1932	134	6	4.6
Strom (207)	1934	121	1	0.8
Moynihan (154)	1932	1000	1	0.1
Eliason & Johnson (61)	1936	163	10	6.1
Friberg (70)	1936	202	11	5.5
Rosing-Bull (191)	1936	69	2	2.9
Perman (66)	1936	187	16	8.5
Eusterman & Balfour (208)	1936	2219	46	2.1
Truesdale (155)	1937	183	9	4.9
Barber & Bagatko (157)	1938	306	20	6.6
St. John et al. (145)	1939	238	23	9.7
Fromme (165)	1939	103	6	5.8
McKirdie & Dulin (158)	1940	85	3	3.5
Heuer (167)	1944	201	8	4.0
Lawson (168)	1945	177	9	5.0
Bruusgaard (71)	1946	416	19	4.7
Ogilvie (159)	1947	124	5	2.1
Douglas (169)	1947	103	4	3.9
Gardner & Hart (160)	1948	68	5	7.3
Walters et al. (171)	1948	88	1	1.1
Total	..	10,274	395	3.8

and pyloroplasty do carry an immediate risk, perhaps of less than 1 or 2 per cent.

MORTALITY RATE OF GASTRIC RESECTION

Reports on the mortality rate of gastric resection for peptic ulcer have been collected and presented in Table 167. In 13,374 patients, the mor-

Table 107

MORTALITY RATE OF GASTRIC RESECTION

Author	Year	Gastric Ulcer			Duodenal Ulcer			Anastomotic Ulcer			Peptic Ulcer		
		No. Cases	No. Died	Per Cent Died	No. Cases	No. Died	Per Cent Died	No. Cases	No. Died	Per Cent Died	No. Cases	No. Died	Per Cent Died
Clairmont (161)	1924							57	10	17.5	243	22	19.0
Flörcken (162)	1924										196	8	4.4
De Takats (172)	1926							41	3	7.3	226	12	5.4
Gatewood (163)	1930	..	..	..	..	..					36	2	5.6
Berg (173)	1930										463	32	7.0
Strauss et al. (174)	1930	..	..	..	221	12	5.4	..	..	..			
Walton (224)	1933							61	16	26.2			
Wright (236)	1935	..	..	..	..	..	..	120	25	20.8			
Perman (66)	1936										97	11	11.3
Fromme (165)	1939	249	18	7.2	294	13	4.4	..	..	..			
Finsterer (175)	1939	..	..	..	..	..	..	194	24	12.2			
Finsterer (176)	1940										1,997	83	4.6
Lawson (168)	1943	53	11	20.9									
Winkelstein (177)	1938										146	6	4.2
McClure & Fallis (178)	1940										74	4	5.2
Wilson (179)	1940										148	12	8.1
Brunsgaard (71)	1946							30	2	6.6	572	23	4.0
Bartels & Dolin (74)	1947										271	24	8.1
Walters et al. (47)	1939				212	4	1.9						
Lake (184)	1948							88	4	11.5	488	29	5.7
Ransom (185)	1947	188	13	7.0									

Douglas (169)	1947	..	..	..	..	..	..	..	..	..	89	9	10.1
Miller (186)	1942	..	..	..	..	..	..	..	..	..	230	7	3.0
Allen & Welch (180)	1946	..	..	..	192	5	2.6	..	..	..	..	..	..
Wells & Brewer (187)	1948	..	..	..	363	9	2.4	..	..	..	..	..	..
Backer-Grøndahl (204)	1944	..	..	..	..	..	..	..	..	..	352	9	2.6
Priestley & Gibson (189)	1948	..	..	..	..	..	..	262*	12	4.6	..	..	..
Rienhoff (44)	1945	..	..	..	260	5	1.9	..	..	..	..	..	..
Rosing-Bull (191)	1943	..	..	..	..	..	..	..	..	..	187	6	3.2
Garlock & Lyons (192)	1949	..	..	..	187	4	2.1	..	..	..	..	..	..
St. John et al. (193)	1948	..	..	..	..	..	..	..	..	..	392	18	4.6
Spak (194)	1948	..	..	..	341	13	3.8	..	..	..	..	..	..
Skinner & Duncan (195)	1948	..	..	..	62	2	3.2	..	..	..	..	..	..
Semb (196)	1945	..	..	..	..	..	..	..	..	..	264	7	2.7
Heuer (167)	1944	59	5	8.4	83	5	6.0	..	..	..	..	..	..
Gardner & Hart (160)	1948	..	..	..	..	..	..	..	..	..	120	8	6.7
Sanders (197)	1945	..	..	..	61	1	1.7	..	..	..	..	..	..
Lahey (188)	1946	110	0	0.0	approx. 400	10	2.6	approx. 100	2	2.2	..	..	..
Visick (86)	1948	93	5	5.4	347	10	2.9	29	1	3.5	505	25	4.9
Gaviser (73)	1948	..	..	..	..	..	..	..	..	..	394	12	3.0
Nicolaysen (200)	1945	..	..	..	..	..	..	..	..	..	290	10	3.4
Bradshaw & Hightower (201)	1947	..	..	..	53	2	3.7	..	..	..	..	..	..
Thompson & Prout (202)	1947	..	..	..	..	..	..	..	..	..	41	11	26.8
Walters et al. (171)	1948	..	..	..	394	7	1.8	63	2	3.2	..	..	..
Plenk & Zeckmann (209)	1948	114	0	0.0	240	3	1.3	12	1	8.5	365	4	1.1
Porter (206)	1948	..	..	..	..	..	..	..	..	..	118	4	3.4
Cooper (30)	1948	..	..	..	..	..	..	27	1	3.7	..	..	..
Doran (205)	1948	..	..	..	..	..	..	26	3	11.5	..	..	..
Total		850	54	6.4	3710	105	2.8	1057	106	10.0	7757	376	4.8

* A few with taking down of gastroenterostomy instead of resection.

All cases total 13,374; deaths, 641; per cent mortality, 4.8.

tality was 4.8 per cent (range, 0 to 30 per cent). The higher rates oc
in the earlier and smaller series. It would appear that experienced surg
geons may today perform the operation with a mortality of less than 2
3 per cent.

Factors Which Influence Mortality Rate. *Site of Ulcer.* Thi
one of the factors, since it would appear that the mortality is lower wh
the resection is done for gastric than for duodenal ulcer. There are pro
bly two reasons for this. First, when the Billroth II type of operation
performed, the most important cause of death is leakage of the duodel
stump, and difficulty in closing the stump seldom occurs in the case
gastric ulcer. Second, the surgeon is inclined to remove more stom
in the case of duodenal ulcer, and this increases the mortality. On
contrary, *an ulcer located high on the lesser curvature*, if removed by the surge
increases the difficulty and mortality of the operation. Some surgeons
not remove such an ulcer if it is likely to make the operation more diffic
since such an ulcer is known to heal after a resection. In several rec
reports, in which the overall mortality is less than 2 per cent, the morta
is less for gastric than duodenal ulcer (171, 188, 203, 209). Several ot
reports are to the contrary (86, 165, 167). However, the overall differen
are not statistically significant.

The mortality from *resection for anastomotic ulcer* is higher than
primary gastric or duodenal ulcer. In a series of 1057 cases collected fr
the literature, the mortality was 10.0 per cent (range 2.2 to 26.2 per ce
(see table 167). The mortality is further increased when the resection
done for an anastomotic ulcer which developed after a previous gas
resection rather than after a previous gastroenterostomy. For example
415 patients resected for an anastomotic ulcer after gastroenterosto
6 per cent died (range, 4.1 to 8.8 per cent); in 73 cases resected afte
previous resection, 17.8 per cent died (range, 0 to 23 per cent) (71, 1
189).

Age. This is another factor which influences the mortality from ope
tion for peptic ulcer, as it does for all operations. Below the age of 40 ye
the mortality from an elective operation in experienced hands is less th
1 per cent (86, 191); between the age of 40 and 60 years, it is 5 per ce
and above 60 years it is from 7.1 to 22.2 per cent (86, 191).

Type of Operation. Little information is available on the comparat
mortalities of the Billroth I and Billroth II operations. In a small series
patients (187), no difference in mortality occurred, although a varia
amount of stomach was resected. Even the advocates of the Billroth
operation find it impossible to use it in every case. Von Haberer (22
up to 1936, used a Billroth I operation in 1946 cases and a Billroth
operation in 1080 cases. In his experience, a Billroth I operation did

olve any greater risk than a Billroth II operation. Persman (222) ved at the same conclusion from a collection of statistics from Swedish pitals.

Mortality Rate of Vagotomy

Reports on the mortality rate of vagotomy are somewhat difficult to lyze, since the operation is frequently combined with anastomotic rations. Authors often do not separate vagotomy alone from vagotomy h drainage operations. We have chosen to determine the mortality e of all vagotomies, with and without other procedures, since the two so frequently combined, except that vagotomy with gastric resection not been included. One group of observers (220) have claimed the rtality of vagotomy and resection is greater than with resection alone other (216) found no apparent increase.

In the 1100 vagotomies reported in the literature (Table 168) and

Table 168

Mortality Rate of Vagotomy*

Author	Year	No. Cases	No. Died	Per Cent Died
Meyer et al. (223)	1948	35	1	2.9
Smith et al. (213)	1948	50	1	0.5
Orr & Johnson (214)	1948	115	0	0.0
Camp & Dragstedt (215)	1948	205	2	1.0
Colp (216)	1948	74	2	2.7
Crile (217)	1948	227	3	1.3
Miller & Olwin (210)	1948	101	0	0.0
Thorek (211)	1949	63	2	3.2
Walters et al. (203)	1949	177	5	2.8
Cameron et al. (212)	1949	53	1	1.9

* Includes some cases with gastroenterostomy or pyloroplasty.

formed for duodenal or anastomotic ulcer, 1.5 per cent died (range, o 3.2 per cent). A significant difference in mortality was not found when operation was performed for a duodenal ulcer or for an anastomotic er following a gastroenterostomy or a gastric resection. No statistically nificant evidence was found showing that the mortality of the abminal approach is different from that of the transthoracic approach.

The 1100 cases of vagotomy collected (Table 168) have been performed since 1944 and by experienced surgeons. Since a gastroenterostomy performed in many of these cases, the mortality from gastroenterosy in experienced hands cannot be over 1.5 per cent.

Mortality Rate of Fundusectomy and Vascular Ligation

Connell (225) reported two hospital deaths among 25 cases of fundusectomy. Somervell (88) had one death among 380 patients on whom the operation of vascular ligation, with or without gastroenterostomy, was done.

Summary

Data for estimating the mortality rate of any or all operations for peptic ulcer in all hospitals are, of course, not available. In experienced hands, it would appear that today the mortality rate of gastroenterostomy or pyloroplasty ranges from 1 to 3 per cent and of gastric resection from 1 to 5 per cent. The mortality rate of gastric resection is probably two or three times greater when it is performed for an anastomotic ulcer following a previous gastric resection. The mortality of vagotomy is probably no higher than that of the operation with which it is combined.

Late Results of Operations on the Stomach

Introduction

In advising an operative procedure, the postoperative incidence of the recurrence of an ulcer with or without hemorrhage, perforation, or death, as well as dyspepsia or abdominal distress, must be considered. Unfortunately, a secure concept of the late satisfactory and unsatisfactory results of the various operations is not easy to obtain. Surgeons and clinics have changed from one operation to another or from gastroenterostomy to gastric resection when their reported late results for gastroenterostomy are as good as those for gastric resection. Yet, gastric resection is still being performed by them.

In order to obtain a comparable idea of the late results of various operative procedures, we have omitted reports with inadequate or short-term follow-up and have reanalyzed and recorded the data of some authors in a form different from that used by them.

Excision of the Ulcer

Simple excision, without additional procedures, has been generally abandoned as a means of surgical treatment of peptic ulcer. Since peptic ulcer is not a locally circumscribed disease, it is not surprising that simple excision was usually followed by a recurrence (66, 75, 168, 224, 227).

Gastroenterostomy

In gastroenterostomy, as in other operations which involve a gastrointestinal anastomosis, recurrences about the anastomosis are the most

frequent and serious cause of unsatisfactory results. Fifty per cent of anastomotic ulcers will occur within one year of the performance of a gastroenterostomy and 70 per cent will occur within two years (Table 119, Chapter 21). For this reason, we feel that the late results of gastroenterostomy cannot be properly appraised without a *minimum* period of follow-up of at least two years. However, in our collective evaluation of gastroenterostomy, some reports have been included when most of the cases appear to have been followed for at least two years.

The method we have chosen for recording late results is one which is frequently used in the literature. An entirely symptom-free patient is said to have an *excellent* result. One who has occasional abdominal complaints, but without evidence of recurrence or loss of time from work, is said to have a *good* result. When the outcome of the operation was excellent or good, the result is *satisfactory*. A *fair* result means the patient is slightly improved, without recurrence of ulcer symptoms, but has some undesirable complications, such as abdominal pain not suggestive of recurrent ulcer, moderate postprandial distress, or severe food dyscrasias. Some have included postoperative hemorrhage not definitely ascribable to a recurrence under fair results. Poor results mean the patient is not better than before operation. All frank recurrences are included under *poor* results. When the outcome of the operation was only fair or poor, the result is *unsatisfactory*.

Gastroenterostomy for Duodenal Ulcer. Satisfactory results were reported in 78 per cent of 2814 patients on whom a gastroenterostomy was performed for duodenal ulcer (Table 169). This percentage may be too high because the operation was abandoned by those who reported poor results and their series were small in number. The average of the percentages of satisfactory results reported by the various authors was 74.8 per cent (range, 37 to 98 per cent).

Sixty per cent of 1660 patients were reported to be symptom-free and 13.5 per cent of 1145 patients were reported to be no better or worse than before operation.

Recurrences occurred in 9.7 per cent of 4122 patients gastroenterostomized for duodenal ulcer, most of the patients being followed for at least two years (Table 170). This recurrence rate may be low because it includes several large series in which a low recurrence rate is reported. The average of the percentages of recurrences reported by the various authors is 14.5 per cent (range, 1.7 to 35.4 per cent).

Most recurrences after gastroenterostomy for duodenal ulcer are anastomotic in site. In 137 cases where the site is provided, 78 per cent were anastomotic, the remainder being chiefly duodenal in location.

Gastroenterostomy for Pyloric Ulcer. Some authors have analyzed their results for duodenal, pyloric, and lesser curvature ulcers.

Table 169

LATE RESULTS OF GASTROENTEROSTOMY FOR DUODENAL ULCER

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*Results*			
				Satisfactory		*Unsatisfactory*	
				Excellent	*Good*	*Fair*	*Poor*
Conybeare (75)	1922	2–11 yr.	30	14 (47%)	8 (27%) 22 (73.3%)	4 (13%)	4 (13%) 8 (26.7%)
Luff (79)	1929	2–9 yr.	669	450 (67%)	149 (22%) 599 (89.5%)	34 (5%)	36 (6%) 70 (10.5%)
Hoffmann (153)	1932	1–7 yr.	107	35 (33%)	28 (26%) 63 (59.8%)	16 (15%)	28 (26%) 44 (40.2%)
St. John et al. (145)	1939	Average of 6 yr.	184	66 (36%)	37 (20%) 103 (56.0%)	30 (16%)	51 (28%) 81 (44%)
Lawson (168)	1945	3–13 yr.	60	22 (37%)	17 (28%) 39 (65.0%)	12 (20%)	9 (15%) 21 (35.0%)
Reid & Marcus (229)*	1948	More than 10 yr.	54	50 (92%)	3 (6%) 53 (98.1%)	0 (0%)	1 (2%) 1 (1.9%)
von Haberer (147)	1918	2 mo.–11 yr.	27		10 (37.0%)	14 (52%)	3 (11%) 17 (63.0%)
Lewisohn (230)†	1925	4–9 yr.	68		32 (47.1%)	13 (19%)	23 (34%) 36 (52.9%)
Tanaseco (149)	1928	1–7 yr.	11	8 (72%)	1 (9%) 9 (81.8%)		2 (18.2%)
Balfour (231)	1930	More than 5 yr.	500	345 (69%)	90 (18%) 435 (87.0%)		65 (13.0%)
Eliason & Johnson (61)	1936	2–5 yr.	70	50 (71%)	8 (11%) 58 (82.9%)		12 (17.1%)
Estes (232)*	1940	3–15 yr.	29	10 (34%)	18 (62%) 28 (96.4%)		1 (3.6%)
Finney et al. (144)	1930	0–30 yr.	67	60 (89.6%)			7 (10.4%)
Douglas (152)	1930	5–12 yr.	68	60 (88.2%)			8 (11.8%)
Crile & Crile (233)	1938	6 mo.–10 yr. (average 3.9 yr.)	54	38 (70.4%)			16 (29.6%)
Barber & Bogatko (157)	1938	1–17 yr.	59	47 (80.0%)			12 (20.0%)
Fromme (165)	1939	1–18 yr.	78	51 (65.4%)			27 (34.6%)
Heuer et al. (167)	1944	2–10 yr.	136	106 (77.9%)			30 (22.1%)
Bruusgaard (71)	1946	More than 2 yr.	189	121 (64.0%)			68 (36.0%)
Douglas (169)	1947	5–11 yr.	52	38 (73.1%)			14 (26.9%)
Ogilvie (159)	1947	5–10 yr.	98	65 (66.3%)			33 (33.7%)
O'Neill (234)	1948	3–11 yr.	150	113 (75.3%)			37 (24.7%)
Gardner & Hart (160)*	1948	1–8 yr.	54	48 (99.9%)			6 (11.2%)
Total	..	..	2814	2198 (78.1%)			616 (21.9%)

* All done for organic pyloric stenosis.

† About one half with pyloric exclusion.

Excellent: of 1660 cases, 1100, or 66.2 per cent, symptom-free.

Poor: of 1145 cases, 154, or 13.5 per cent, no better or worse than before operation.

Average per cent of satisfactory results: 74.8.

Table 170

RECURRENCES* AFTER GASTROENTEROSTOMY FOR DUODENAL ULCER

Author	Year	Duration of Follow-up	Posterior Gastroenterostomy		Anterior Gastroenterostomy		Undifferentiated Gastroenterostomy	
			No. Followed	No. Recurrences	No. Followed	No. Recurrences	No. Followed	No. Recurrences
Lewisohn (230)†	1925	4–9 yr.	..	..	..	..	68	23 (33.8%)
Luff (79)	1929	2–9 yr.	..	..	..	..	669	21 (2.9%)
Balfour (231)	1930	More than 5 yr.	..	..	..	..	500	20‡(4.1%)
Wright (236)	1935	5–10 yr.	1730	147 (8.5%)	85	8 (9.4%)	..	..
Eliason & Johnson (61)	1936	3 mo.–14 yr.	..	..	..	..	128	11§(8.5%)
Barber & Bogatko (157)	1938	1–17 yr.	..	..	..	..	59	1 (1.7%)
Crile & Crile (233)	1938	6 mo.–10 yr.	54	1 (1.8%)	..	..	..	..
St. John et al. (145)	1939	Average 6 yr.	184	40¶(21.7%)	..	..	..	..
Fromme (165)	1939	1–18 yr.	..	..	..	..	78	27 (34.6%)
Graham (237)	1940	..	..	..	..	..	48	17|| (35.4%)
Lawson (168)	1945	3–13 yr.	..	..	..	..	60	9 (15.0%)
Douglas (169)	1947	5–11 yr.	..	..	..	..	52	10 (19.2%)
O'Neill (234)	1948	3–11 yr.	..	..	..	..	150	13 (8.7%)
Cooper (30)	1948	1–14 yr.	257	49**(19.1%)	..	..	..	..
Total	..	..	2225	237 (10.6%)	85	8 (9.4%)	1812	152 (8.4%)

* Primarily anastomotic ulcers but also a few recurrent or persistent duodenal or gastric ulcers.
† About one half with pyloric exclusion.
‡ Sixteen anastomotic, and four recurrent gastroduodenal ulcers.
§ Six anastomotic and five recurrent gastroduodenal ulcers.
¶ Twenty-four anastomotic, and 16 recurrent gastroduodenal ulcers.
|| Fourteen anastomotic, and three recurrent gastroduodenal ulcers.
** Forty-six anastomotic, and three recurrent gastroduodenal ulcers.

Table 171

LATE RESULTS OF GASTROENTEROSTOMY FOR PYLORIC ULCER

Author	Year	Duration of Follow-up	No. Cases Followed	Results	
				Satisfactory	Unsatisfactory
Conybeare (75)	1922	2–11 yr.	25	18 (72.0%)	7 (28.0%)
Tanaseco (149)	1928	1–7 yr.	19	14 (74.5%)	5 (26.5%)
Luff (79)	1929	2–9 yr.	296	274 (92.5%)	22 (7.5%)
Barber & Bogatko (157)	1948	1–7 yr.	80	61 (76.3%)	19 (24.7%)
Total	..	..	420	367 (87.4%)	53 (12.6%)

Average of reported percentages of satisfactory results = 78.8 per cent (range, 72 to 93 per cent).

Satisfactory results were reported in 87.4 per cent of 420 cases of gastroenterostomy for pyloric ulcer. This percentage is probably too high because unusually good results were reported for one series which included a large number of patients. The average of the percentages of satisfactory results reported by the various authors is 78.8 per cent (range, 72 to 93 per cent).

On referring to Table 171, it will be noted that the late results of gastroenterostomy for pyloric and for duodenal ulcer are quite similar in the case of the same author. This might be expected on the basis of the fact that gastroenterostomy diverts acid chyme away from the ulcer at either site to the same extent.

Table 172

LATE RESULTS OF GASTROENTEROSTOMY FOR GASTRIC ULCER

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*Results*			
				Satisfactory		*Unsatisfactory*	
				Excellent	*Good*	*Fair*	*Poor*
Conybeare (75)	1922	2–11 yr.	39	5 (38%)	8 (21%)	7 (18%)	9 (23%)
				13 (59.0%)		16 (41.0%)	
Hoffmann (153)	1932	1–7 yr.	21	7 (33%)	4 (19%)	5 (24%)	5 (24%)
				11 (52.4%)		10 (47.6%)	
St. John et al. (145)	1939	Average 3.5 yr.	13	3 (23%)	0 (0%)	4 (31%)	6 (46%)
				3 (23.1%)		10 (76.9%)	
Heuer (167)	1944	1½–10 yr.	29	20 (69%)	4 (14%)	2 (7%)	3 (11%)
				24 (82.7%)		5 (17.3%)	
Lawson (168)	1945	3–13 yr.	35	13 (37%)	15 (43%)	5 (14%)	2 (6%)
				28 (80.0%)		7 (20.0%)	
Tanaseco (149)	1928	1–7 yr.	17	9 (53%)	2 (12%)		
				11 (64.7%)		6 (35.3%)	
Finney et al. (144)	1930	0–30 yr.	46	35 (76.1%)		11 (23.9%)	
Douglas (152)	1930	5–12 yr.	27	21 (77.8%)		6 (12.2%)	
Balfour (231)	1930	More than 5 yr.	100	79 (79.0%)		21 (21.0%)	
Barber & Bogatko (157)	1948	1–17 yr.	28	20 (71.4%)		8 (18.6%)	
Bruusgaard (71)	1946	More than 2 yr.	45	28 (62.2%)		17 (37.8%)	
Douglas (169)	1947	5–11 yr.	9	5 (55.6%)		4 (44.4%)	
Ogilvie (159)	1947	5–10 yr.	9	5 (55.6%)		4 (44.4%)	
O'Neill (234)	1948	3–11 yr.	19	13 (68.4%)		6 (21.6%)	
Total	..	..	437	306 (70.0%)		131 (30.0%)	

Average percentage of satisfactory results = 64.8 (range, 23 to 83 per cent).

GASTROENTEROSTOMY FOR GASTRIC ULCER. The late results of gastroenterostomy for gastric ulcer are shown in Table 172. The results represent ulcers referred to by various authors either as "gastric ulcers" or as "ulcers of the lesser curvature."

Satisfactory results are reported in 70 per cent of 437 patients. The average of the percentages of satisfactory results reported by the various authors is 64.8 per cent (range, 23 to 83 per cent).

Thirty-seven per cent of 154 patients were symptom-free and 18.2 per cent of 137 patients were no better or worse than before operation.

Recurrences occurred in 8.6 per cent of 806 patients (Table 173). The

Table 173

RECURRENCES AFTER GASTROENTEROSTOMY FOR GASTRIC ULCER

Author	*Year*	*Duration of Follow-up*	*No. Followed*	*No. Recurrences*	*Per Cent Recurrences*
Balfour (231)	1930	More than 5 yr.	100	3	3.0
Wright (236)	1935	5–10 yr.	592	54	9.1
Barber & Bogatko (157)	1938	1–17 yr.	28	2	7.1
St. John et al. (145)	1939	Average 3.5 yr.	13	0	0.0*
Heuer (167)	1944	1½–10 yr.	29	4	13.8
Lawson (168)	1945	3–13 yr.	35	2	5.7
Douglas (169)	1947	5–11 yr.	9	4	44.4
Total			806	69	8.6

* No recurrent anastomotic ulcer.

Average percentage of recurrences = 11.9 (range, 0 to 44.4 per cent).

average of the percentages of recurrences reported by the various authors is 11.9 per cent (range, 0 to 44.4 per cent). This percentage may not be high enough because some authors did not include persistent ulcers on the lesser curvature, which were not uncommon and probably accounted for some unsatisfactory results.

Satisfactory results occur less frequently after gastroenterostomy for gastric than for duodenal ulcer, though the difference is not striking or statistically significant. This tendency, however, may be explained by indicating that gastroenterostomy cannot divert much, if any, acid chyme away from an ulcer of the lesser curvature, as it may and can do in the case of an ulcer of the duodenum or pyloric canal.

GASTROENTEROSTOMY FOR PEPTIC ULCER. Satisfactory results were reported in 2194, or 72.7 per cent, of 3016 cases in which it was not stated whether the gastroenterostomy was performed for a gastric or duodenal ulcer. The average of the percentages of the satisfactory results reported

by the various authors is 71.2 per cent (range, 54 to 92 per cent). As might be expected, the 73 per cent of satisfactory results lies between the 70 per cent for gastric and 78 per cent for duodenal ulcer (Table 174).

Table 174

LATE RESULTS OF GASTROENTEROSTOMY FOR PEPTIC ULCER

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*Results*	
				Satisfactory	*Unsatisfactory*
				Excellent / *Good*	*Fair* / *Poor*
Horsley (143)	1930	0–10 yr.	50	31 (62%) 7 (14%) 38 (76.0%)	6 (12%) 6 (12%) 12 (24.0%)
Emery & Monroe (80)	1935	More than 3 yr.	258	54 (23%) 104 (44%) 158 (66.4%)	15 (6%) 65 (27%) 80 (33.3%)
Friberg (70)	1936	0–16 yr.	131	54 (41%) 38 (29%) 92 (70.2%)	27 (21%) 12 (9%) 39 (29.8%)
von Eiselsberg (146)	1914	2–8 yr.	230	134 (58.3%)	46 (20%) 50 (21.7%) 96 (41.7%)
Clairmont (161)	1924	1–20 yr.	289	162 (56.1%)	31 (11%) 96 (33.3%) 127 (43.9%)
Flörcken (162)	1924	Average 9.3 yr.	133	96 (72.2%)	23 (17%) 14 (10.8%) 37 (27.8%)
Paterson (150)	1926	3–13 yr.	447	316 (71%) 94 (21%) 410 (91.7%)	37 (8.3%)
DeTakats (172)	1926	1–10 yr.	274	137 (50%) 60 (22%) 197 (71.9%)	77 (28.1%)
Gatewood (163)	1930	5–15 yr.	146	100 (68%) 25 (17%) 125 (85.6%)	21 (14.4%)
Church & Hinton (38)	1940	More than 1 yr. (average 7.1 yr.)	93	24 (26%) 26 (28%) 50 (53.8%)	43 (46.2%)
Pool & Dineen (148)	1922	1–7 yr. (average 2 yr.)	59	50 (84.7%)	9 (15.3%)
Solkov & Iljun (242)	1927	More than 3 yr.	580	441 (76.0%)	139 (24.0%)
Lake (219)	1928	1–6 yr.	71	45 (63.4%)	26 (36.6%)
Perman (66)	1936	More than 3 yr.	143	93 (65.0%)	50 (35.0%)
Truesdale (155)	1937	0–30 yr.	132	102 (77.3%)	30 (22.7%)
Total			[illegible]	[illegible]	823 (27.5%)

Average percentage of satisfactory results: 71.2 (range, 54 to 93 per cent).
Excellent: of 1379 cases, 716, or 51.9 per cent, symptom-free.
Poor: of 1071 cases, 243, or 22.7 per cent, no better or worse than before operation.

Seven hundred sixteen, or 51.0 per cent, of 1379 patients were reported as symptom-free and 243 or 22.7 per cent of 1071 patients were no better or worse than before operation. Recurrences occurred in 292, or 10.3 per cent, of 2828 patients (Table 175). The average of the percentage of recurrences reported by the various authors is 11.5 per cent (range, 1.1 to 30 per cent).

Table 175

RECURRENCES AFTER GASTROENTEROSTOMY FOR PEPTIC ULCER

Author	Year	Duration of Follow-up	No. Followed	No. Recurrence	Per Cent Recurrence
...on Eiselsberg (146)	1914	2–8 yr.	230	7	3.0
...ool & Dineen (148)	1922	1–7 yr.	59	2	3.4
...onybeare (75)	1922	2–11 yr.	84	7	8.5
...on Haberer (243)	1922	0–13 yr.	275	3	1.1
...Jarmont (161)	1924	1–20 yr.	314	81*	25.8
...aterson (150)	1926	3–13 yr.	447	12	2.7
...urst & Stewart (244) †	1929	0–19 yr.	131	25	19.1
...atewood (163)	1930	5–15 yr.	146	11	7.5
...mery & Monroe (60)	1935	More than 3 yr.	238	27	11.3
...riberg (70)	1936	0–16 yr.	131	2	1.5
...erman (66)	1936	More than 3 yr.	143	18	12.5
...ruesdale (155)	1937	0–30 yr.	132	5	3.8
Church & Hinton (38)	1940	More than 1 yr. (average 7.1 yr.)	106	26	24.4
Bruusgaard (71)	1946	More than 2 yr.	234	40‡	17.1
...Linn (245)	1946	..	30	9	30.0
Gardner & Hart (160) §	1948	1–8 yr.	54	3	5.6
...Sangster (246)	1948	..	74	14	18.9
Total			2828	292	10.3

* Twenty anastomotic ulcers and 61 recurrent gastroduodenal ulcers.
† Autopsy material.
‡ Nineteen anastomotic ulcers and 21 recurrent gastroduodenal ulcers.
§ For organic pyloric stenosis.

FACTORS WHICH INFLUENCE RESULTS AFTER GASTROENTEROSTOMY. *Pyloric Exclusion.* The combination of pyloric exclusion (247) with gastroenterostomy (Fig. 134, 5) rendered the late results more unfavorable. Only 58 per cent of 212 patients obtained satisfactory results and 23.5 per cent suffered a recurrence, almost all being located at the anastomosis (Table 176). The incidence of anastomotic ulcers is higher than with simple gastroenterostomy because the entire brunt of acid chyme is placed on the jejunum.

Devine's operation (Fig. 134, 6) consists of a pyloric exclusion with an end-to-side Polya type of gastroenterostomy. Only one report of the results of this operation with a satisfactory follow-up is available. This report is by Gray and Sharp (40), who observed that 21 of 50 patients so operated for bleeding ulcer suffered further bleeding or an anastomotic ulcer (see also (33)).

Table 176

LATE RESULTS FOLLOWING GASTROENTEROSTOMY WITH PYLORIC EXCLUSION FOR PEPTIC ULCER

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*Results*		*Recurrences**
				Satisfactory	*Unsatisfactory*	
von Haberer (147)	1918	2 mo.–11 yr.	44	30 (68.2%)	14 (31.8%)	..
Tanaseco (149)	1928	1–7 yr.	35	24 (68.6%)	11 (31.4%)	..
Clairmont (161)	1924	1–20 yr.	65	33 (50.8%)	32 (49.2%)	24 (36.9%)
Emery & Monroe (60)	1935	More than 3 yr.	31	18 (58.1%)	13 (41.9%)	5 (16.1%)
Perman (66)	1936	More than 8 yr.	37	18 (48.6%)	19 (51.4%)	9 (24.3%)
von Haberer (243)	1922	0–13 yr.	71	..	..	12 (16.9%)
DeTakats (172)	1926	1–10 yr.	85	..	..	18 (21.2%)

* Almost all anastomotic ulcers.
In 212 cases, 123 (58.0 per cent) satisfactory results.
In 212 cases, 89 (42.0 per cent) unsatisfactory results.
In 289 cases, 68 (23.5 per cent) recurrences.

En-Y and Enteroenteroanastomosis. Both of these procedures (Fig. 134, *3*, *4*) divert the duodenal juices away from the gastrojejunal anastomosis and deprive the jejunal mucosa of the neutralizing and diluting action of the pancreatic juice and bile. These procedures are analogous to the M-W operation in dogs. When such a procedure has been used, an incidence of anastomotic ulcer ranging from 15.5 to 37.5 per cent has been reported (66, 236, 250).

Anterior and Posterior Gastroenterostomy. Since the jejunal mucosa shows a cephalad to caudad gradient of susceptibility to acid, one would expect a short-loop posterior gastroenterostomy to result in a low incidence of recurrences. Unfortunately, the clinical data concerning the relation of the length of the jejunal loop is meager and inconclusive. According to Wright's (236) collective survey, 8.5 per cent of 1730 patients with a posterior gastroenterostomy (Fig. 134, *2*) and 9.4 per cent of 85 patients with an anterior (Fig. 134, *1*) developed an anastomotic ulcer. Paterson (150) found that 4.1 per cent of 96 patients with a posterior and 2.3 per cent of 347 patients with an anterior gastroenterostomy developed an anastomotic ulcer. These differences are not impressive.

Selection of Patients. In a major portion of the period in which gastroenterostomy was the standard operative procedure for peptic ulcer, a large percentage of patients were treated surgically in some clinics. No doubt many patients with "mild ulcers" who represented a type successfully treated medically today were operated on. Thus, some of the variations in the percentages of satisfactory results or recurrences may be

attributed to this factor, especially in view of the fact that some clinics performed a gastroenterostomy for duodenitis.

Thirteen hundred and twenty-seven cases of gastroenterostomy for duodenal or peptic ulcer have been reported since 1939. In these cases, the indications for surgery presumably were the same as those for gastric resection today. There were recurrences in 257, or 19.4 per cent (30, 38, 71, 145, 160, 165, 168, 169, 234, 237, 245, 246).

The factor of the duration of the disease probably affects the surgical results in the same way as it does the medical results. The factor of preoperative acidity, which has been discussed elsewhere, operates only in that it determines the level of postoperative acidity. Pain and hemorrhage as indications for operation do not appear to be related significantly to the incidence of unfavorable results (Table 177).

Table 177

INFLUENCE OF REASON FOR OPERATION ON RESULTS OF GASTROENTEROSTOMY

Author	*Reason for Operation*	*Number of Followed Cases*	*Duration of Follow-up*	*Number Satisfactory*	*Per Cent Satisfactory*
Crile & Crile (233) (Duodenal ulcer)	Hemorrhage	5	6 mo.–10 yr.	4	80
	Obstruction	16	" "	14	88
	Pain	33	" "	20	61
St. John et al. (145) (Duodenal ulcer)	Hemorrhage	32	Average of 6.3 yr.	13	41
	Obstruction	63	" " 5.4 yr.	51	81
	Pain	87	" " 6.3 yr.	39	44
Douglas (169) (Duodenal ulcer)	With obstruction	15	5–11 yr.	12	80
	Without obstruction	37	" "	26	70
Church & Hinton (38) (Peptic ulcer)	With obstruction	19	More than 1 yr.	12	63
	Without obstruction	74	" " "	38	51
Cooper (30) (Duodenal ulcer)	Hemorrhage	76	1–13 yr.	57	75
	Obstruction	124	" "	105	85
	Pain	70	" "	59	84
Total	With obstruction	237		194	82.3
	Without obstruction	414		256	61.8

The presence of organic pyloric stenosis is a condition which has frequently been considered to prognosticate a high percentage of satisfactory results. This is supported by the results recorded in the literature, which indicate that 82.3 per cent of 237 patients with obstruction obtained satisfactory results, whereas only 61.8 per cent of 256 patients without

obstruction did so. This statistically significant difference is supported by the observations of several other authors (158, 160, 229, 232). This difference may be due to the possibility that long-standing pyloric stenosis leads to gastritis and a lowered gastric acidity in a sufficient number of cases to decrease the incidence of recurrences and unsatisfactory results. Other authors, without presenting adequate evidence, deny the difference and, appropriately, argue that gastric resection is the operation of choice in patients with obstructing ulcers or lesions, because the incidence of postoperative ulcer is lower for gastric resection than for gastroenterostomy in the presence of obstructing lesions.

Sex. Bruusgaard (71) and Perman (66) have reported observations which show that males experience satisfactory results significantly more frequently after gastroenterostomy than females. The explanation of this is not clear.

Age. Bruusgaard (71) and Cooper (30) present data showing that from 82 to 91 per cent of patients over 60 years of age report satisfactory results after gastroenterostomy. This is generally explained as being related to the decreased secretion of acid with age. The cause of the unsatisfactory results after gastroenterostomy will be considered later (p. 1022).

Pyloroplasty for Peptic Ulcer

Many ways to widen the pyloric outlet have been used in the treatment of peptic ulcer (Fig. 134, *7*, *8*). The Heineke-Miculicz and Horsley pyloroplasty and the Finney gastroduodenostomy are designed for this purpose primarily. Judd, however, designed his pyloroplasty to include excision of the ulcer of the anterior wall of the duodenum. Today, few of these anterior wall ulcers are subjected to operation because they usually respond so well to medical therapy.

The late results of the various pyloroplasties are not comparable because the results on so few cases in each group have been reported. Also, very little information is available on the persistence or recurrence of the ulcer after pyloroplasty.

Satisfactory results have been reported in 81.6 per cent of 691 patients. The average of the percentage of satisfactory results of various authors is 68.2 per cent (range, 37 to 92 per cent). The figure of 81.6 per cent may be too high because the series of patients of Judd and Hazeltine (142) make up more than one half of the patients and the period of follow-up was relatively short. This interpretation is supported by Balfour (251) from the same clinic, who seven years later wrote that "enough recurrences of symptoms and even ulcer following any of the operations on the outlet of the stomach make it obvious that this type of operation should be performed only under special circumstances." (See Table 178.)

Table 178

LATE RESULTS OF PYLOROPLASTY FOR PEPTIC ULCER

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*Satisfactory*		*Unsatisfactory*	
				Excellent	*Good*	*Fair*	*Poor*
Horsley (143)	1930	6 mo.–10 yr.	72	26 (33%)	9 (12%) 35 (48.7%)	9 (12%)	28 (36%) 37 (51.3%)
Emery & Monroe (60)	1935	More than 3 yr.	54	10 (19%)	27 (50%) 37 (68.5%)	6 (11%)	11 (20%) 17 (31.5%)
St. John et al. (145)	1939	Average 4.0 yr.	21	9 (43%)	4 (19%) 13 (62.0%)	4 (19%)	4 (19%) 8 (38.0%)
Judd & Hazeltine* (142)	1930	1–5 yr.	363	333 (91.7%)		30 (9.3%)	
Finney & Hanrahan (144)	1930	0–30 yr.	*For Duodenal Ulcer* 106	92 (86.7%)		14 (13.3%)	
			For Gastric Ulcer 56	47 (83.9%)		9 (16.1%)	
Perman (66)	1936	More than 3 yr.	19	7 (36.8%)		12 (63.2%)†	
Total	..	..	691	564 (81.6%)		127 (18.4%)	
Total, excluding Judd & Hazeltine	..	..	328	231 (70.4%)		97 (29.6%)	

* Balfour, from the same clinic, reporting in 1937 stated that pyloroplasty was seldom indicated because of the high incidence of recurrences.

† Ten, or 53 per cent, recurrences.

Average percentage of satisfactory results = 68.2; without Judd and Hazeltine, 64.4.

Thirty per cent of 147 patients remained symptom-free and 29.2 per cent were no better or no worse. Perman (66) reported that 53 per cent of 19 patients developed recurrences and probably most of the 29.2 per cent just referred to had a recurrence.

Further surgery for a recurrent ulcer is indicated only if the recurrence does not respond to medical management.

GASTRIC RESECTION

INTRODUCTION. Several factors influence the late results of gastric resection.

One factor is the length of the period of follow-up, the *minimum* period of which should be at least two years, because only 70 per cent of the recurrences occur within that period. We have included in our statistics only those reports in which the majority of patients have been followed for at least two years.

The extent of the resection should be correlated with the incidence of recurrences, since the operation is done chiefly to decrease gastric acidity. Several authors have presented some data showing that such is the case (87, 187, 193, 252), since the results were unsatisfactory in from 20 to 34 per cent of cases when little more than a pylorectomy was performed. Removal of one half of the stomach resulted in 12 per cent unsatisfactory results by Heuer (167). In our statistics, we have included only those cases in which at least one half of the stomach has been removed.

The results of gastric resection have been evaluated as was done in the case of gastroenterostomy (p. 1002).

Gastric Resection for Duodenal Ulcer. Satisfactory results were obtained in 92.7 per cent of 1487 patients, the majority of whom were followed for more than two years. The average of the percentage of satisfactory results of the various authors is 92.2 per cent (range, 81.6 to 98.2 per cent). In so far as possible, cases in which a portion of the pylorus

Table 179

Late Results of Gastric Resection for Duodenal Ulcer

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*Results*	
				Satisfactory	*Unsatisfactory*
				Excellent / *Good*	*Fair* / *Poor*
Watson (69)	1947	6 mo.–8 yr.	68	28 (41%) 35 (51%) 63 (92.7%)	2 (3%) 3 (4%) 5 (7.3%)
Spak (194)	1948	More than 1 yr. (average 4.1 yr.)	102	70 (69%) 21 (21%) 91 (89.2%)	8 (8%) 3 (3%) 11 (10.8%)
Gaviser (73)	1948	2–7 yr.	231	48 (21%) 175 (76%) 223 (96.5%)	8 (3.5%)
Allen & Welch (180)	1946	1–14 yr.	107	74 (69%) 26 (23%) 100 (93.5%)	7 (6.5%)
Berg (254)	1933	1–10 yr.	225	218* (96.9%)	7 (3.1%)
Walters et al. (182)	1940	1–10 yr.	197	192 (97.5%)	5 (2.5%)
Heuer (167)	1944	2–10 yr.	29	25 (86.2%)	4 (13.8%)
Rienhoff (44)	1945	2–10 yr.	255	208 (81.6%)	47† (18.4%)
Sanders (197)	1945	1–11 yr.	48	43 (89.6%)	5 (10.4%)
Douglas (169)	1947	5–11 yr.	11	10 (90.9%)	1 (9.1%)
Mimpriss & Birt (255)	1948	1–6 yr.	100	94‡ (94.0%)	6 (6.0%)
Wells & Brewer (187)	1948	2–13 yr.	114	112 (98.2%)	2 (1.8%)
Total	..	..	1487	1379 (92.7%)	108 (7.3%)

* Twenty-three with mild general symptoms.

† Includes 26 cases requiring reoperation, although classified as satisfactory by the author.

‡ Some with mild postprandial distress.

Average percentage of satisfactory results: 92.2.

Of 475 cases, 220, or 46.3 per cent, symptom-free.

was not removed were excluded from this group of cases regardless of whether the mucosa was or was not excised (see Table 179).

Only 46.3 per cent of 475 patients (range, 21 to 69 per cent) were reported to be symptom-free. The remainder of those with satisfactory results suffered mild, transient abdominal discomfort, probably due to the loss of the reservoir function of the stomach.

Recurrences, proved or suspected, occurred in 5.1 per cent of 2048 patients, the majority of whom were followed for two years or more. The average of the percentage of recurrences reported by the various authors is 4.1 (range, 0 to 11.2) (Table 180). Almost all of the recurrences were

Table 180

RECURRENCES FOLLOWING GASTRIC RESECTION FOR DUODENAL ULCER

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*No. Recurrences*	*Per Cent Recurrences*
Wright (236)	1935	5–10 yr.	109	3	2.8
Walters et al. (182)	1940	1–10 yr.	197	5	2.5
Mage (256)	1942	1–17 yr.	502	40	8.0*
Kiefer (41)	1942	More than 1 yr.	143	16	11.2*
Sanders (197)	1945	More than 1 yr.	48	4	8.3
Rienhoff (44)	1945	2–10 yr.	255	23	9.0
Allen & Welch (180)	1946	1–14 yr.	129	3	2.3
Watson (69)	1947	6 mo.–8 yr.	68	3	4.4
Douglas (169)	1947	5–11 yr.	11	0	0.0
Gaviser (73)	1948	More than 2 yr.	231	4	1.7
			⅔ to ¾ Resection		
Visick (86)	1948	More than 2 yr.	93	3	3.2
			More than ¾ Resection		
Wells & Brewer (187)	1948	..	148	0	0.0
			114	0	0.0
Total	..	..	2048	104	5.1

* Includes late postoperative bleeding.

anastomotic, since the resection was performed basically by the Billroth II procedure.

GASTRIC RESECTION FOR GASTRIC ULCER. The late results of gastric resection for gastric ulcer appear to be better than for duodenal ulcer. This is probably related to the higher incidence of achlorhydria.

Satisfactory results were reported in 95.2 per cent of 499 patients (Table 181). The average of the percentage of satisfactory results reported by the various authors is 95.9 (range, 90 to 100).

Sixty-four per cent of 269 patients were symptom-free. Recurrences

occurred in only 1.1 per cent of 954 patients (Table 182). The average of the reported percentages of the various authors is 1.4 (range, 0 to 7). The ulcers recurred in the stomach or at the anastomosis.

Table 181

LATE RESULTS OF GASTRIC RESECTION FOR GASTRIC ULCER

Author	Year	Duration of Follow-up	No. Cases Followed	Results			
				Satisfactory		Unsatisfactory	
				Excellent	Good	Fair	Poor
Ransom (183)	1947	2–20 yr.	138	65 (48%)	62 (42%)	7 (5%)	4 (3%)
				127 (92.0%)		11 (8.0%)	
Watson (69)	1947	6 mo.–8 yr.	59	22 (37%)	35 (59%)		
				57 (96.6%)		2 (3.4%)	
Gaviser (73)	1948	2–7 yr.	72	55 (76%)	15 (21%)		
				70 (97.2%)		2 (2.8%)	
Berg (254)	1933	1–10 yr.	49	48* (98.0%)		1 (2.0%)	
Heuer (167)	1944	2–10 yr.	28	27 (96.4%)		1 (3.6%)	
Sanders (197)	1945	9 mo.–9 yr.	10	10 (100.0%)		0 (0.0%)	
Douglas (269)	1947	5–11 yr.	40	36 (90.0%)		4 (10.0%)	
Mumpriss & Burt (255)	1948	1–6 yr.	103	100 (97.1%)		3 (2.9%)	
Total			499	475 (95.2%)		24 (4.8%)	

* Includes four patients with "mild general symptoms."

Of 269 cases, 172, or 64 per cent, symptom-free.

Average percentage of satisfactory results: 95.9.

GASTRIC RESECTION FOR PEPTIC ULCER. Some authors have reported their results only as "peptic ulcer." Satisfactory results were reported in 90.3 per cent of 924 patients. The average of the percentages reported by the various authors is 89.9 (range 84 to 96) (Table 183). Seventy per cent of 437 patients were reported symptom-free.

Recurrences occurred in 2.1 per cent of 1607 patients. The average of the recurrences reported by the various authors is 2.5 per cent (range 0.6 to 5 per cent) (Table 184).

FACTORS INFLUENCING RECURRENCE RATE AND PERCENTAGE SATISFACTORY RESULTS AFTER RESECTION. *Size of Resection.* It has been previously indicated on the basis of meager evidence and *a priori* reasoning that the recurrence rate is usually high and the percentage of satisfactory results correspondingly low when a very limited partial gastrectomy is done. Thus, there are some surgeons who advocate resection of three-quarters of the stomach, while others believe that resection of one half to two thirds of the stomach is sufficient. In gastric ulcer, the size of the

Table 182

RECURRENCES FOLLOWING GASTRIC RESECTION FOR GASTRIC ULCER

Author	Year	Duration of Follow-up	No. Cases Followed	No. Recurrences	Per Cent Recurrences
(236)	1933	1–10 yr.	44	1*	2.3
(236)	1935	5–10 yr.	516	3	0.6
(167)	1944	2–10 yr.	28	0	0.0
(197)	1945	3 mo.–3 yr.	19	0	0.0
(69)	1940	6 mo.–8 yr.	53	0	0.0
(165)	1947	5–11 yr.	40	3	7.5
(183)	1947	2–20 yr.	138	3†	2.2
(73)	1942	2–3 yr.	72	0	0.0
		3/4 to 3/4 Resection			
(86)	1948	More than 2 yr.	21	0	0.0
		More than 3/4 Resection			
			20	0	0.0
Total			951	10	1.1

* Recurrent gastric ulcer.
† Anastomotic ulcers.
Average percentage of recurrences = 1.4.

Table 183

LATE RESULTS OF GASTRIC RESECTION FOR PEPTIC ULCER

Author	Year	Duration of Follow-up	No. Cases Followed	Results			
				Satisfactory		Unsatisfactory	
				Excellent	Good	Poor	Poor
Sloan & Priddle (178)	1949	0–5 yr.	44	36 (82%)	25 (57%)	4 (9%)	1 (2%)
				61 (86.7%)		5 (11.3%)	
et al. (191)	1949	5–10 yr.	371	171 (71%)	46 (12%)	27 (8%)	20 (5%)
				226 (70.5%)		47 (13%)	
(134)	1937	2–13 yr.	198	141 (82.4%)		29 (17.6%)	
& Hinton (43)	1941	More than 1 yr.	97	88 (90.7%)		9 (9.3%)	
		average 3 yr.					
& Dodds (174)	1947	2½–5 yr.	92	88 (95.7%)		4 (4.3%)	
& Harr (146)	1948	0–8 yr.	100	88 (88%)		12 (12%)	
			934	836 (89.5%)		98 (10.5%)	

Average percentage of satisfactory results = 89.5.
Of 437 cases, 89.8 per cent symptom-free.

resection does not seem as important as in duodenal ulcer, for the recurrence rate is so low with either two thirds or three quarters of the stomach resected.

Table 184

RECURRENCES FOLLOWING GASTRIC RESECTION FOR PEPTIC ULCER

Author	*Year*	*Duration of Follow-up*	*No. Cases Followed*	*No. Recurrences*	*Per Cent Recurrences*
Clairmont (161)	1924	1–10 yr.	160	6	3.7
Perman (66)	1936	More than 3 yr.	76	1	1.3
Lake (258)	1937	2–15 yr.	242	5	2.5
Church & Hinton (43)	1942	More than 1 yr. (average 2.9 yr.)	104	2	1.9
Bruusgaard (71)	1946	More than 2 yr.	364	7*	2.0
Bartels & Dulin (74)	1942	2½–5 yr.	92	4	4.3
Gardner & Hart (160)	1948	0–8 yr.	100	5	5.0
Steinberg (260)	1948	0–23 yr. (85 per cent followed more than 1 yr.)	319	2	0.6
Grove & Rasmussen (261)	1948	0–10 yr.	150	2	1.3
Total	..	..	1607	34	2.1

* Three anastomotic ulcers, three recurrent ulcers, and one hemorrhage.
Average percentage of recurrences = 2.5.

Unfortunately, there is at present no good means for determining the amount of stomach resected. What is actually important is the amount of stomach left in and not the amount removed. The amount of stomach resected is determined by weighing the amount of stomach resected or by a guess of the surgeon. The use by some surgeons of the bare vascular area above the gastroepiploic vessels or other vascular landmarks (86) as a point of transection might prove to be an accurate method of determining the amount of stomach removed or left behind.

Some reports have used these various criteria to estimate the amount of stomach removed. For duodenal or peptic ulcer, some have resected from 55 to 70 per cent of the stomach in all cases (44, 69, 86, 167, 197, 261). In 638 such cases, 5.8 per cent had recurrences. Others have resected three quarters of the stomach in all cases of duodenal or peptic ulcer (73, 180, 187, 198, 256, 260). In 1443 such resections, 50, only 3.5 per cent, had recurrences. The difference is significant ($\chi^2 = 6.0$), and we may assume that the recurrence rate is lower when three quarters of the stomach is resected. However, if Steinberg's cases are omitted because of

the uncertainty of the care of the follow-up, there are 1124 cases with 4.3 per cent recurrences, and the difference between 5.8 and 4.3 per cent is not significant, though in the anticipated direction.

Choice between Billroth I and Billroth II Gastric Resection. There are very few reports dealing with the Billroth I type of operation (Fig. 134, *9*, *10*), although a few European surgeons (221, 270) have used the procedure extensively. On a theoretical basis the procedure is excellent, since it reëstablishes gastrointestinal continuity in a normal anatomic fashion. It also places the duodenum, which is less susceptible to ulceration than the jejunum, next to the stomach.

However, most surgeons throughout the world, and particularly those who advocate subtotal resections, employ modifications of the Billroth II gastric resection (Fig. 134, *12-14*) for two reasons. *First*, they feel that an anastomosis of the stomach to a scarred or inflamed duodenum is not only difficult but also dangerous. Some compromise and use a Billroth I operation for gastric ulcer and a Billroth II for duodenal ulcer. *Second*, the objection is raised that a gastroduodenal anastomosis following resection of two thirds or three quarters of the stomach is very difficult and the suture line is put under tension. Those who object to the Billroth I operation also fear that the situation may be compromised by a smaller resection.

Length of Jejunal Loop. As shown elsewhere, considerable experimental evidence indicates that the incidence of anastomotic ulcers should be lower when a short jejunal loop is used. Unfortunately, an accurate evaluation of the length of the jejunal loop is not possible from the literature because of variations in the size of resections. Nevertheless, the impression is gained that those surgeons who use a short-afferent-loop posterior gastrointestinal anastomosis have a lower incidence of anastomotic ulcer.

Method of Handling Nonresectable Duodenal Ulcers. Some ulcers of the duodenum are so adherent to an adjacent viscus or those of the second part of the duodenum are so close to the ampulla of Vater that their removal is dangerous or the typical inversion closure of the duodenum is impossible. Reports in the literature regarding the incidence of ulcer not resected vary from 1 (271) to 75 per cent (44). With increasing experience, the incidence of ulcers considered not to be resectable may decrease. For instance, Finsterer (176) reported that nonresectable ulcers constituted 16.6 per cent of his operative material in an early report, but the figure dropped to 6.0 per cent in a later report. The experience of Flörcken (272) is similar. In his early cases, 20 per cent of ulcers were not removed, but later only 10 per cent. Ruge (273) found that he left 80.0 per cent of duodenal ulcers behind in early resections, but only 3.3 per cent in later cases.

Various Alternatives to a Typical Gastroduodenal Resection. The most popular

alternatives to typical gastroduodenal resections are: (1) Finsterer's resection with pyloric exclusion (Fig. 134, *B*) (or with exclusion of the ulcer by transecting the duodenum proximal to the ulcer as suggested by Förcker); (2) Finsterer's resection with pyloric exclusion and excision of the pyloric mucosa (Fig. 134, *C*); (3) a two stage gastric resection in which a gastric resection with antral exclusion is performed as a first stage and the antrum resected at a second operation in two or three months; (4) gastroduodenal resection with an atypical duodenal closure; (5) simple gastroenterostomy; and (6) vagotomy.

Some authors apparently have been able to include the duodenal ulcer in all their resections by using an atypical duodenal closure (271). However, one suspects that the operative mortality may have been slightly increased. Atypical closures are apt to be complicated by damage to the biliary tree, pancreatitis, or duodenal fistulas, which may prove fatal. The principal advantage of resections which leave the ulcer behind is the greater safety in the closure of the duodenal stump. The risks of such operations are hemorrhage or perforation of the ulcer in the immediate postoperative period, or failure to attain late satisfactory results. However, hemorrhage or perforation in the immediate postoperative period are quite rare (194). These complications may be due to extensive dissection of the duodenum prior to deciding that the ulcer cannot be safely removed (252).

Gastric Resection with Pyloric Exclusion. Finsterer (106), in his initial description of resection with pyloric exclusion, suggested excision of the mucosa, although he did not routinely do so for several years. Willkinson (275) "rediscovered" the procedure in 1926, and Bancroft (276) in 1935 suggested that the mucosa be excised in conjunction with the Devine operation. The mucosa is now excised routinely by most surgeons when any of the pyloric portion of the stomach is left in place. The wisdom of this is established by the following late results. An anastomotic ulcer (proved or suspected) occurred in 39 per cent of 123 patients in whom the pyloric mucosa was not excised and in only one of 79 patients in whom the mucosa was excised (Table 185).

Excision of the duodenal ulcer is favored by some (11, 277), whereas others believe that the results are just as good when it is left behind if the pyloric mucosa is excised (73, 165, 176, 180, 194). The results after the excision of the pyloric mucosa are so good that it is not necessary to excise the ulcer, especially when the ulcer is not readily excisable.

Some have performed the exclusion operation without removal of the mucosa, and then at a second operation have removed the pyloric portion of the stomach (279). The mucosa is so easily excised that a second operation seems unnecessary.

High-lying Gastric Ulcer. The risk of gastric resection is increased when for gastric ulcers high on the lesser curvature. In order to include ulcer in the resection, a nearly total gastrectomy must be performed, a modification of the Shoemaker operation is used with a large curvature and smaller greater curvature resection.

Table 185

RECURRENCES FOLLOWING RESECTION WITH PYLORIC EXCLUSION

Author	Year	Duration of Follow-up	No. Cases Followed	Number Recurrences	Per Cent Recurrences
Without Excision of Pyloric Mucosa					
...e (262)	1938	More than 2 yr.	22	9	40.9
...r (41)	1942	More than 1 yr.	30	7	23.3
... & Welch (252)	1942	2–11 yr.	9	5	55.6
...berg (263)	1947	..	14	3	21.4
...er (73)	1948	2–7 yr.	6	3	50.0
...ner & Hart (160)	1948	0–8 yr.	11	1	9.1
... & Brewer (187)	1948	More than 2 yr.	31	20	64.5
...tal	..	..	123	48	39.0
With Excision of Pyloric Mucosa					
... & Welch (252)	1942	2–11 yr.	12	0	0.0
...ner & Hart (160)	1948	0–8 yr.	12	0	0.0
...er (73)	1948	2–7 yr.	55	1	1.8
...tal	..	..	79	1	1.3

Some (280) have reported excellent results with the Madlener type section, in which a typical gastric resection is done but the line of section of the stomach is below the ulcer, which is left in the gastric ...p. It has been objected that this procedure would fail to remove the ..., which might be malignant. However, the risk of removing the ... may actually be higher than the risk of malignancy.

Medical therapy should certainly be given a thorough trial in high- ... gastric ulcers. Those who recommend a vagotomy for these cases ...mmend a radical resection if the ulcer fails to heal after the vagus ...es have been sectioned. Intensive medical therapy seems a better ...ce than vagotomy to us.

Obstructing Ulcer. Whether the patient has an obstructing or nonob- ...ting ulcer, the results of gastric resection appear to be the same.

Gaviser (73) reported that 94 per cent of 82 obstructed and 97 per cent of 282 nonobstructed patients experienced satisfactory results after a two to seven year follow-up. Sanders (197) reported similar results on a smaller group of patients.

Enteroenterostomy and En-Y Anastomosis. This predisposes to an anastomotic ulcer as it does when a gastroenterostomy is performed. For instance, Finsterer (175) reported 13 recurrences in 21 patients subjected to a resection and an en-Y anastomosis.

Sex. Bruusgaard (71) and Perman (66) obtained less satisfactory results in females than males, as they did in the case of gastroenterostomy, but the differences were not significant. Gaviser (73) found no difference, since 96 per cent of 305 males and 97 per cent of 59 females experienced satisfactory results after a resection.

Age. Bruusgaard (71) obtained 84 per cent of satisfactory results in 74 patients older than 50 years and in 235 patients younger than 50 years. Age made no difference in his group.

Cause and Treatment of Unsatisfactory Results after Gastroenterostomy and Gastric Resection. *Anastomotic and Recurrent Ulcer.* The most distressing result following gastroenterostomy or gastric resection is anastomotic ulcer, although in a few cases an ulcer at the preoperative site persists or recurs.

Many anastomotic ulcers are treated by some medical procedure, as is shown by the unverified or suspected cases in most reports. Some authors believe that "surgical intervention is the only therapy to be considered" (33, 189, 281). Finsterer (175) has written: "The significant difference in the mortality rates following radical operations for gastrojejunal ulcer, 8.1 per cent when appearing after gastroenterostomy, and 23.5 after resections, should determine the indications for management of recurrent ulcers." He advised resection for gastrojejunal ulcer following gastroenterostomy, and a trial of medical therapy for a gastrojejunal ulcer following a gastric resection. If the treatment failed, he advised a gastric resection. Most physicians of experience, with whom we concur, believe that medical therapy should be tried, unless perhaps when the ulcer is adherent to the colon (282–286, 288). The same holds for painless bleeding.

Medical Therapy of Anastomotic Ulcer: This is the same as for a gastric or duodenal ulcer, except that it is more strict, as a rule. It is generally recognized that the results are more unsatisfactory, but the data reported in the literature are relatively meager. Of 117 cases of anastomotic ulcer treated medically, but with a relatively short follow-up, only 31 per cent experienced a satisfactory result. The average of various authors ranges from 7 to 60 per cent (71, 283, 285–287).

Medical treatment is indicated in every case, but, in view of the danger

of perforation, gastrojejunal fistula, and hemorrhage (Chapter 21), the treatment should not be temporized, keeping in mind the mortality of an operation.

Conservative Operative Procedures for Anastomotic Ulcer: These have not been very satisfactory. Local excision has a low initial mortality but does nothing toward preventing a recurrence. Hence, the few late results reported are quite unsatisfactory (224, 236). Dismantling of the gastroenterostomy and reconstruction of the normal passageway also are attended by a low mortality but unsatisfactory results. In 177 such patients, only 38 per cent reported satisfactory results for a variable period of follow-up (66, 168, 236, 283, 287, 289, 290). *Most of these patients developed a recurrence of the duodenal ulcer, which shows that the diversion of acid chyme had been of benefit.*

Gastric Resection for Anastomotic Ulcer: This results in a relatively high mortality (p. 1000), though the late results are apparently quite good. In 86 per cent of 545 patients, the results were satisfactory. Unfortunately, in some of the cases the duration of follow-up and the amount of stomach resected were not given (Table 186), and the late results may not be as favorable as these figures indicate.

Gastric Resection with Pyloric Exclusion for Peptic Ulcer: This results in a relatively high incidence of recurrent anastomotic ulcer if the mucosa of the pyloric portion of the stomach is not removed (p. 1020).

Table 186

LATE RESULTS OF GASTRIC RESECTION FOR ANASTOMOTIC ULCER

Author	*Duration of Follow-up*	*No. Cases Followed*	*Results*	
			Satisfactory	*Unsatisfactory*
Bruusgaard (71)	More than 2 yr.	18	12 (67%)	6 (33%)
von Haberer (221)	..	113	95 (84%)	18 (16%)
Makkas (265)	..	47	40 (85%)	7 (15%)
Finsterer (175)	0–20 yr.	55	50 (91%)	5 (9%)
Walton (224)	0–16 yr.	45	44 (97%)	1 (3%)
Wright (236)	5–10 yr.	91	81 (89%)	10 (11%)
Cooper (30)	Average 3.4 yr.	26	19 (62%)	7 (38%)
Douglas (169)	5–10 yr.	5	4 (80%)	1 (20%)
Perman (66)	More than 3 yr.	16	10 (63%)	6 (27%)
Priestley & Gibson (189)	5–10 yr.	103	90 (87%)	13 (13%)
Doran (205)	..	21	16 (76%)	5 (24%)
Watson (69)	6 mo.–8 yr.	5	5 (100%)	0 (0%)
Total	..	545	466 (86%)	79 (14%)

A number of anastomotic ulcers which have occurred after this oper tion have been cured by resection of the pyloric remnant; a few failur have also been reported. For example, in 34 patients treated with reso tion of the pyloric remnant alone, satisfactory results occurred in 29 a unsatisfactory in five (15 per cent) (63, 71, 160, 187, 252, 279, 291).

Though more data are needed to provide a firm answer to this im portant question, it would appear that in the presence of an adequa resection, excision of the excluded pyloric remnant alone should be th operation of choice because it should be accompanied by a low mortalit in contrast to the relatively high mortality of a second gastric resectio The importance of resecting the excluded pyloric remnant is illustrate by the report of a case in which vagotomy failed to cure the patient, thoug a subsequent resection of the pyloric remnant did (131).

Vagotomy for Anastomotic Ulcer: Vagotomy has been done in 11 patients, according to our survey of the literature, and the patients we followed from zero to 43 months after the operation. The results we satisfactory in 83 per cent of the patients. A longer follow-up will b required to reveal the late results (Table 187).

The literature is conflicting regarding the comparative benefit vagotomy for anastomotic ulcer following gastroenterostomy and gastr resection. The number of cases is very small, however (189, 216, 266).

Vagotomy appears to be especially applicable to the operative trea ment of anastomotic ulcer because it is attended with a low mortality The ultimate results are as yet uncertain.

Hemorrhage. Bleeding is a frequent cause of unsatisfactory results follow ing anastomotic operations on the stomach. This is particularly true whe the original ulcer has bled (p. 973).

While postoperative hemorrhage frequently can be ascribed to recurrent or anastomotic ulcer, it may occur in the absence of pain an an x-ray demonstrable ulcer. In such cases, it is generally agreed that th bleeding is due to superficial acute ulcers or erosions in the mucosa of th jejunum or stomach (153, 296). Good statistics are not available on th point because of the assumptions involved when the patient has not bee examined by operation or at least by gastroscopy. Some authors includ hemorrhage cases with cases of recurrence of ulcers without hemorrhag assuming that all cases of hemorrhage are due to an ulcer. There are no enough cases of painless bleeding after gastric resection, or even afte gastroenterostomy, reported to give the relative incidence of bleedin with or without pain or a proven ulcer. For example, Mage (296) foun that of 23 patients who bled after gastric resection, 15, or 65 per cent, ble painlessly, whereas Kiefer (141) reported that 40 per cent of 20 patient with recurrence of pain or bleeding bled without having a demonstrabl ulcer.

Table 187

LATE RESULTS OF VAGOTOMY FOR ANASTOMOTIC ULCER

Author	Duration of Follow-up	No. Cases Followed	Recurrences	Severe and Persistent Motility Disturbances	Results	
					Satisfactory	Unsatisfactory
			Anastomotic ulcer following gastroenterostomy			
lp (216)	4–24 mo.	10	1	0	9 (90%)	1 (10%)
			Anastomotic ulcer following gastric resection			
		15	5	0	10 (67%)	5 (33%)
			Anastomotic ulcer following gastroenterostomy			
inson et al. (266)	7–43 mo.	10	0	1	9 (90%)	1 (10%)
			Anastomotic ulcer following gastric resection			
		9	0	3	6 (67%)	3 (33%)
			Anastomotic ulcer following gastroenterostomy			
estley & Gibson (189)	0–18 mo.	22	..	..	20 (91%)	2 (9%)
			Anastomotic ulcer following gastric resection			
		16	..	..	15 (94%)	1 (6%)
oore et al. (131)	0–2 yr.	10	1*	0	9 (90%)	1 (10%)
tey (268)	0–2½ yr.	5	0	0	5 (100%)	0 (0%)
ithy (374)	7–21 mo.	2	1	1	0 (0%)	2 (100%)
ller & Olwin (210)	0–2 yr.	9	1	2	6 (67%)	3 (33%)
agstedt et al. (269)	0–3 yr.	10	0	1	9 (90%)	1 (10%)
Total	..	118	..	..	98 (83%)	20 (17%)

* Cured by antral excision at a later operation.

In 80 cases where the information is given, nine, or 11 per cent, had recurrences.

In 51 cases where the information was given, eight, or 11 per cent, had severe and istent motility disturbances.

Regarding treatment, Mage [296] believes that bleeding without may be treated medically and bleeding with pain should be tre surgically. We believe that medical management should also be gi thorough trial in the latter group.

Postchal or Postprandial Distress. Following gastric resection, app mately 11 per cent (range, 3 to 30 per cent) of patients experience dis after eating (Table 188). In some patients, the symptoms occur dura

Table 188

INCIDENCE OF POSTPRANDIAL DISTRESS FOLLOWING SUBTOTAL GASTRIC RESECTION

Author	*All Cases of Postprandial Distress*			*Severe or Disabling Postprandial Distress*		
	No. Cases	No.	Per Cent	No. Cases	No.	Per Cent
Brimsgaard [71]	364	58	15.6	364	5	1.4
Custer et al. (303)						
Series I	500	28	5.6	500	16	3.2
Series II	112	14	12.5			
Mateer (305)			14.0			
Allen & Welch (55)	129	39	30.0*	129	3	2.3
Gaviser (73)	416	11	2.6†			
Ransom (183)	147	21	14.3	147	1	0.7
Smith & Jordan (52)	167	23	13.8‡			
Total	1835	192	10.5	1140	25	2.2

* Symptoms referrable to too small size of stomach or too rapid filling of intest

† Mild to moderate "dumping syndrome."

‡ 6.6 per cent dumping syndrome and 7.2 per cent postprandial fullness

soon after eating, which is referred to as "*early postchal distress.*" In oth the distress occurs an hour or two after eating and is referred to as "*postchymous distress.*" Early distress is more common than late distr although both types may occur in the same patient [297–301].

Incidence: *The actual incidence* of postchal distress after gastric resec is difficult to ascertain. Some patients learn quickly to avoid the disc fort by making changes in the daily mode of living and eating, and be do not report its occurrence (71). In some patients, the symptoms ar mild that their presence has to be elicited by specific questioning. example, in a study (303) of 500 cases, the incidence was found to be per cent and in another study by the same authors on 112 cases specific interrogation the incidence was 12.5 per cent. The distress is severe in

only approximately 2.2 per cent of patients (range, 0.7 to 3.2 (Table 166).

on the incidence of postulal distress after gastroenterostomy available, although all agree that the incidence of early postulal is less than after resection. It was first described under the expres- the "dumping stomach" by Mix in 1921 (320). The symptoms also ter a pyloroplasty or an anastomosis of the stomach to the duo- 239, 301, 303).

ptoms: The symptoms of *early postulal distress* may be discussed the headings of "the syndrome of the dumping stomach," which for most cases, and "the syndrome of the small stomach."

"*yndrome of the dumping stomach*" is characterized by weakness, , flushing, warmth and perspiration, epigastric fullness, cardiac ion, and nausea. These symptoms may occur after a small amount is swallowed or 10 or 15 minutes after eating. They do not always ter every meal and are usually most severe after sweet foods. The ms are frequently self limiting because the patient soon learns how t them. In other patients, the symptoms are more distressing than ating peptic ulcer, and it is in these cases that the condition is dy to persist (303).

" syndrome of the small stomach" is characterized by a sensation ent fullness or pressure after eating, sometimes with slight nausea. drome usually disappears with time.

symptoms of late postulal distress are those of hypoglycemia. , hunger, feeling of emptiness, weakness, and perspiration, and ally relieved by food.

logy: The "syndrome of the dumping stomach" is probably due to on or irritation of the jejunum or a combination of both. In such he gastric remnant does empty rapidly (303, 313, 314), but no pidly than in some patients who have no symptoms (71, 315). This hat rapid emptying alone is not an adequate cause in all patients t that the symptoms may be produced by the ingestion of small of hypertonic solutions, particularly sugar, before any change in ugar occurs shows that irritation is a factor (300, 314). This ob- n is reinforced by the report that sweet food predisposes to the ce of the symptoms (314). We observed many years ago (321) symptoms of the dumping stomach may occur not only when the um is irritated with cold, hypertonic, and chemically irritating s, but also when distended with a balloon and when lukewarm, bland pabulum is introduced too rapidly. These facts also apply g through a jejunal fistula. This is much less likely to occur when e solution is introduced into the stomach (321). Similarly, in

patients with the symptoms of a dumping stomach, distension of the gastric remnant does not cause the symptoms (303), whereas distension of the jejunum does (314).

It has been suggested that the early symptoms are due to a "hyperglycemic shock" (316) for two reasons. First, because a hyperglycemia tends to occur soon after meals in patients with gastroenterostomy, and, second, because it has been claimed that the introduction of levulose into the jejunum will not cause the symptoms. However, it seems unlikely that hyperglycemia is related to early postprandial distress, since others have found that hypertonic levulose can cause the symptoms, that even when the symptoms are produced with glucose, they occur before the blood sugar level rises, that the symptoms may occur in the absence of hyperglycemia, and that the symptoms do not occur when hyperglycemia is produced by the intravenous injection of glucose (300). Undoubtedly, a jejunitis would predispose to the development of symptoms from distension or from any source of physical or chemical irritation; this appears to be the most likely cause of the "syndrome of the dumping stomach."

The symptoms of the late postcibal distress are probably due to hypoglycemia (297, 299, 300, 310–312), one of the reasons being that they are usually relieved by food. Carbohydrates in the form of cooked starches and especially sugars are readily digested and absorbed on being emptied rapidly from the stomach. This causes a hyperglycemia, which in some persons is followed by hypoglycemia. Hypoglycemia with symptoms may be produced in some patients by the glucose tolerance test, although a history of spontaneous symptoms may be lacking (312).

Treatment: Surgically, an attempt has been made to prevent rapid emptying of the gastric remnant. Statistically insignificant results have been reported, which suggest that the use of the Hofmeister valve or a decrease in the size of the stoma (255, 303, 322) reduces the incidence of symptoms from a dumping stomach. Experimental evidence as well as clinical opinion have been published to support the view that the size of the stoma does not affect the emptying of the gastric remnant (324–326). The Hofmeister valve (Fig. 134, *13*), which decreases the size of the stoma as compared to the Polya procedure (Fig. 134, *14*) by closing a portion of the gastric remnant by suturing from the lesser to the greater curvature, also tends to prevent filling and distension of the afferent loop, which is claimed to decrease the incidence of postoperative symptoms (255). This is not substantiated with adequate data.

The medical management of the late symptoms is to instruct the patient to prevent them by taking some food prior to their anticipated occurrence. Evensen (312) has reported that the symptoms are more likely to be produced if the patient exercises after the meal, rest being a prophy-

lactic measure. It has also been suggested that meals low in carbohydrate should be advised to prevent a "reactive hypoglycemia" (298).

The management of the dumping stomach may at first involve the use of a bland, soft diet with one of the aluminum gels to act as a demulcent and slightly astringent preparation for an irritated jejunum. Frequent feedings are indicated to prevent undue distension and substances such as sugars, which make a hypertonic solution readily, and any other known offender should be avoided. Cold or hot foods should also be avoided. In some patients, any liquid food is poorly tolerated. Lying down after meals is often effective, since the gastric remnant does not empty so rapidly (71). The patient should be studied carefully to determine the consistency and character of the foods best tolerated.

The postcibal distress due to a "small stomach" is best managed by placing the patient on frequent feedings until the gastric remnant hypertrophies.

Atropine has yielded various results (295, 303, 314). It has been recommended for the late hypoglycemic symptoms also and has yielded variable results (300, 316, 317). The use of ephedrine has been suggested (303). Bruusgaard (71) has used doryl and Stein (318) has used doryl or urecholine with success. These parasympathomimetic drugs apparently act by increasing the tone of the jejunum and preventing its distension. A sedative is sometimes required by the tense and excitable patient as a bridge to the development of a calm attitude of mind.

Food Intolerances. A number of patients have specific food intolerances following gastric resection. These complaints overlap with postprandial distress. Milk and sweet foods constitute the usual foods which are poorly tolerated, although a few patients have multiple food intolerances. Gaviser (73) noted that 35 per cent of 364 subtotally gastrectomized patients had difficulty with only one food, while 4.4 per cent observed dietary restrictions for multiple foods. Ransom (183) found that 27 per cent of 138 patients had specific food intolerances following subtotal gastrectomy for gastric ulcer. These patients do well, since they learn to avoid those foods which cause nausea or upper abdominal distress.

Weight Changes after Gastric Resection and Gastroenterostomy. A significant number of patients have difficulty in maintaining their preoperative weight after anastomotic operations for peptic ulcer. This is particularly true after gastric resection. Some patients who have difficulty in maintaining their weight suffer from complications, such as postprandial distress or recurrence of the ulcer, but many of the patients are able to work and are essentially asymptomatic aside from the inability to gain weight.

Following gastric resection, 40 or 50 per cent of patients are unable to maintain their average preoperative weight (Table 189). Some of these

Table 189

POSTOPERATIVE WEIGHTS AFTER GASTRIC RESECTION COMPARED TO AVERAGE PREOPERATIVE WEIGHT

Author	*No. Cases*	*Postoperative Weight*		
		Less than Average Preoperative Weight	*No Change*	*More than Average Preoperative Weight*
Ransom (183)	112*	75%	13%	12%
Gaviser (73)	352†	36%	7%	57%
Smith & Jordan (52)	146	16%	..	..
Allen & Welch (55)	129‡	67%	10%	23%
Church & Hinton (43)	97§	48%	13%	39%
Strauss et al. (315)	28	21%	..	79%
Total	864	47%¶	10%	43%

* Seventy-five per cent lost an average of 17 pounds and 12 per cent gained an average of 10 pounds. The overall average showed an 11.7 per cent weight loss.

† Thirty-six per cent lost an average of 11 pounds and 57 per cent gained an average of 13.5 pounds.

‡ Males lost an overall average of six pounds. Females lost an overall average of 13 pounds.

§ Overall average showed a fraction of a pound gain.

¶ Forty-two per cent including series of Smith and Jordan.

patients are actually below their optimum weight. Similar data are not available for weight changes following gastroenterostomy.

Smith and Jordan (52) reported weight changes in patients who had gastric resections for gastric ulcer. In 70 cases followed less than two years, 11.4 per cent failed to gain weight; in 51 cases followed two to five years, 9.8 per cent failed to gain, and in 46 cases followed more than five years, 21.7 per cent failed to gain weight. On the other hand, Santy and Mallet-Guy (333) found that patients who were unable to gain weight in the first year or two after operation usually gained thereafter. They believe that frequency of the inability to gain weight diminishes as length of time after operation increases.

Patients who have had a gastric resection for an obstructed ulcer usually gain weight after the operation, since they are poorly nourished preoperatively.

The cause of the inability to gain weight is associated with impairment of the digestion and absorption of food. Following gastric resection, and also gastroenterostomy to some extent, most patients show a greater loss

of ingested fat in the feces than is normal (71, 334, 336, 338). In most cases, the excess excretion of fat is small, although in a few cases it may be many times normal. Fecal loss of proteins and carbohydrates also occurs occasionally.

Since many patients develop achlorhydria after gastric resection, it might be thought that the inability to digest and absorb foodstuffs, particularly fat, is associated with the diminished flow of pancreatic secretions or bile. However, the stools of patients with spontaneous achlorhydria or achylia gastrica are usually normal. It is probable that the rapid emptying of the stomach and rapid intestinal passage seen in patients with gastroenterostomy or resection play an important role.

Reinhoff (44) and Allen and Welch (55) state that the "gourmet" seldom has difficulty maintaining his weight. Animals in whom a total gastrectomy has been performed may be maintained at an optimum weight by careful diet. Because of the absence of the reservoir function of the stomach, they eat slowly, but are able to ingest enough calories (338). The administration of pancreatin in adequate amounts to gastrectomized dogs decreases the fecal wastage and renders the maintenance of weight much less difficult. This should be tried in patients.

Patients in whom the loss of weight presents a problem frequently can gain weight by increasing their caloric intake. Some have difficulty in eating a large meal because of the small size of the stomach. In such cases, small, frequent, nutritious meals are advisable.

Anemia Following Gastric Resection and Gastroenterostomy. Pernicious Anemia: Castle (339) has clearly demonstrated that the gastric juice, acting in conjunction with beef muscle, yeast, etc., can form some substance which causes remission of pernicious anemia. Yet total removal of the stomach of laboratory animals is not followed by pernicious anemia (335, 341). Not many cases of pernicious anemia have been reported in human beings following total removal of the stomach. Indeed, some of the cases reported doubtfully fulfill the criteria of pernicious anemia. Almost all cases which developed pernicious anemia did so two to 15 years after the operation (342, 343).

The incidence of pernicious anemia following partial or subtotal gastrectomy for peptic ulcer is certainly low. In 1851 cases of gastric resection for peptic ulcer followed from six months to 20 years, only four, or about 0.2 per cent, of the cases developed anemia of the pernicious type (52, 69, 71, 73, 86, 183, 258, 346, 349, 351, 352). In patients with unexplained gastric anacidity on whom gastric operations have not been performed, the chance of developing pernicious anemia is about three per thousand, or 0.3 per cent (355).

Similar figures on the incidence of pernicious anemia following gastro-

Table 190

HYPOCHROMIC AND NORMOCHROMIC ANEMIA AFTER GASTRIC RESECTION

Author	*Criterion of Anemia (Hb Means Hemoglobin)*	*No. of Cases*	*Anemic*	*Not Anemic*
Morley & Roberts (346)	Hb less than 70 per cent	68	25 (37%)	43
Gordon-Taylor et al. (336)	Hb less than 80 per cent in males & less than 70 per cent in females	52	23 (44%)*	29
Gaviser (73)	Hb less than 12.5 Gm. per cent	347	46 (13%)†	301
Rieder (349)	Hb less than 80 per cent	162	98 (60%)‡	64
Dedichen (352)	Hb less than 80 per cent	164	83 (51%)	81
Larsen (360)	Hb less than 90 per cent in males & less than 80 per cent in females (13.8 Gm. per cent = 100 per cent)	86	44 (51%)§	42
Bruusgaard (71)	Hb less than 90 per cent in males & less than 80 per cent in females (13.8 Gm. per cent = 100 per cent)	307	101 (25%)¶	206
Watson (69)	..	122	14 (12%)	108
Smith & Jordan (52)	..	157	22 (14%)	135
Rosenthal & Abel (351)	Hb less than 80 per cent	117	16 (14%)	101
Total	..	1582	472 (30%), of which about 14 per cent are borderline anemias	1110 (70%)

* Eight males, or 15 per cent, with Hb between 70 and 80 per cent.

† Twenty-eight, or 8 per cent, with Hb between 11.0 and 12.5 Gm. per cent.

‡ Fifty-nine, or 36 per cent, with Hb between 70 and 80 per cent.

§ Fourteen males, or 16 per cent, with Hb between 80 and 90 per cent.

¶ Eight males, or 15 per cent, with Hb between 80 and 90 per cent.

enterostomy are not available; however, Addisonian anemia has been reported in a few cases (71, 244, 356, 358).

Hypochromic Anemia: Although hyperchromic anemia is rare following gastric resection and gastroenterostomy, anemias with a low or normal color index are common. Some totally gastrectomized animals develop an "iron deficiency" type of anemia spontaneously; others only when they are placed under stress, such as secondary infection, diarrhea, or pregnancy (338).

In the varied reports on the incidence of hypochromic anemia following gastric resection (Table 190) and gastroenterostomy (Table 191) for

Table 191

HYPOCHROMIC AND NORMOCHROMIC ANEMIA AFTER GASTROENTEROSTOMY

Author	*Criterion of Anemia (Hb Means Hemoglobin)*	*No. of Cases*	*Anemic*	*Not Anemic*
Larsen (360)	Hb less than 90 per cent in males & less than 80 per cent in females (13.8 Gm. per cent = 100 per cent)	65	23 (35%)*	42
Bruusgaard (71)	Hb less than 90 per cent in males & less than 80 per less in females (13.8 Gm. per cent = 100 per cent)	165	34 (21%)†	131

* Ten males, or 15 per cent, with Hb between 80 and 90 per cent.
† Eight males, or 5 per cent, with Hb between 80 and 90 per cent.

peptic ulcer, most have indicated as anemic those patients with a postoperative hemoglobin level of less than 80 per cent. Since the average hemoglobin of females in the general population is lower than that of males, a few authors have set the minimum limit of "normal" slightly lower for operated females than for operated males. Unfortunately, many authors have not designated the number of grams of hemoglobin per 100 cc. of blood which constitutes "100 per cent." The best method of reporting hemoglobin levels is in terms of grams per 100 cc. of blood rather than in terms of per cent.

In Table 190, the postoperative blood pictures of 1582 patients who have had gastric resection for ulcer are collected. Thirty per cent have been classified as anemic, although about one half of the anemic cases are only slightly below the lower limit of normal.

Only two well documented reports (71, 360) dealing with the postoperative blood picture of gastroenterostomy are available (Table 191). Of 230 cases, about 25 per cent were said to be anemic. Almost one half

of these cases had borderline anemia. The incidence of anemia was found to be slightly less with gastroenterostomy than with gastric resection (71, 360).

The sex of the patient is important in determining the occurrence of postoperative anemia. Females are much more prone to develop anemia even when provision is made for their usually lower average hemoglobin. In the case of gastroenterostomy, 21 per cent of 149 males were classified as anemic and 32 per cent of 81 females (71, 360). While the difference is not quite significant ($\chi^2 = 3.1$), the difference is in the expected direction considering the results of gastric resection. In the case of gastric resection for peptic ulcer, 20 per cent of 762 males were anemic postoperatively while 53 per cent of 321 females were anemic postoperatively (69, 71, 72, 336, 352, 360). The difference is highly significant.

Because most of the iron is absorbed in the upper part of the small intestine, anemia should occur more frequently in those patients whose stomach empties rapidly and who have a chronic diarrhea. Since iron is more soluble in an acid medium, it is not surprising that the incidence of anemia has been reported to be higher in patients who have an achlorhydria postoperatively (71, 360).

In patients with chronic diarrhea, the possibility of the development of vitamin, protein, and calcium deficiencies must be kept in mind.

The treatment of the anemia or the deficiency is no different than that found in other conditions, such as gastrogenic diarrhea and nutritional deficiency. Most anemias respond to oral ferrous sulfate, although a few may fail to do so (361). Gastrectomized animals respond better to iron administered parenterally than orally, and parenteral iron therapy may be necessary in those patients who respond poorly to iron orally.

Other Deficiencies. Calcium deficiency is best treated by giving soluble calcium salts (calcium lactate or gluconate) with the meals (362). Vitamin deficiencies, when found, are best remedied by giving them parenterally at first and later orally with the food. Protein hydrolysates are less likely to irritate the intestinal mucosa when mixed with other food, such as cereal.

Results of Vagotomy for Peptic Ulcer

Introduction. Partial vagotomy for peptic ulcer has been performed with indifferent results (122, 363). In 1943 Dragstedt and Owens (364) properly and for the first time placed the emphasis on the importance of complete vagotomy.

It is very difficult to evaluate the results of vagotomy for several reasons. *First*, many articles dealing with the subject do not provide a follow-up study of longer than a few months, although the results have

een termed satisfactory because the patients experienced prompt relief om ulcer symptoms. This is a gratifying result but, as discussed under nedical management, prompt relief of distress is an inadequate criterion or testing the value of a therapy for peptic ulcer. One only has to recall he prompt relief of ulcer symptoms which so frequently follows a simple astroenterostomy. *Second*, a minimum period of follow-up of any therapy or peptic ulcer should be long enough to include most of the recurrences. n the case of gastric resection, 70 per cent of the recurrences occur within wo years postoperatively, but a similar period for vagotomy has yet to be stablished. In a series of only six cases, Illingworth and Kay (366) reported that all had prompt relief of pain, but one recurred at six months, wo at 18 months, and one at two years, two not having recurred in three ears. This meager series is referred to chiefly to emphasize the paucity of reports now available on this phase of the results of vagotomy. *Third*, nd more important as regards the difficulty of the evaluation of the esults of vagotomy, is the fact that vagotomy is frequently performed with simple gastroenterostomy or a pyloroplasty, some believing that a drainage operation should be done routinely and others only when pyloric tenosis is present or likely to occur. In evaluating the results of vagotomy, t would appear to be necessary to differentiate the results of vagotomy alone and vagotomy combined with other procedures. So few cases of gastric resection combined with vagotomy have been reported and the follow-up is so short that we have excluded this procedure from our consideration. *Fourth*, vagotomy may produce motor disturbances of the alimentary tract, some of which are severe and persistent and require a secondary drainage operation or gastric resection. These must be classified as unsatisfactory in evaluating the results. *Fifth*, in some patients it is difficult to cut all the branches of the vagi, according to the results of the "insulin test." In 160 patients operated by Harper and Dragstedt (367), 11.2 per cent received an incomplete vagotomy. The fact that recurrence of an ulcer is more frequent in such patients is of much scientific significance, but must be considered as an unsatisfactory result and a disadvantage of the operation. *Sixth*, the ulcer symptoms, when they recur after vagotomy, vary in severity. In some, the symptoms are typical, but an ulcer crater cannot be demonstrated (203, 266, 368); in a few patients, an ulcer crater may be detected in the absence of typical ulcer symptoms (266, 368). Such patients with symptomatic or roentgenologic evidence of recurrence have usually been classified under unsatisfactory results.

Rate of Healing. Lastra and Nobo (371) found that nine ulcer craters after vagotomy disappeared in an average of 44 days (range, 20 to 90 days), although all experienced prompt relief of pain. This is the same average found in medical management from bed-rest and a soft,

bland diet with an antacid (p. 911). On the other hand, Grimson et al. (266) observed two anastomotic ulcers which required a year and a half to two years to heal after vagotomy!

VAGOTOMY FOR DUODENAL, GASTRIC, PEPTIC, AND ANASTOMOTIC ULCER. Vagotomy *alone* when performed for duodenal ulcer yielded satisfactory results in 77 per cent of 292 patients who had been followed for from zero to five years (Table 192). The average period of follow-up was

Table 192

VAGOTOMY FOR DUODENAL ULCER (VAGOTOMY ALONE)

Author	*Duration of Follow-up*	*No. Cases Followed*	*No. Recurrences*	*No. Severe and Persistent Motility Disturbances*	*Results*	
					Satisfactory	*Unsatisfactory*
Colp (216)	9–20 mo.	18	3	5	12 (67%)	6 (33%)
Dragstedt & Camp (373)	2½–5 yr.	55	3	4	45 (82%)	10 (18%)
Moore (368)*	5–45 mo.	116	13	5% (about 6)	97 (84%)	19 (16%)
Smithy (374)	7 mo.–2 yr.	8	2	0	6 (75%)	2 (25%)
Walters et al. (203)	0–3 yr.	26	..†	..	17 (65%)	9 (35%)
Miller & Olwin (210)	0–2 yr.	27	1	4	22 (81%)	5 (19%)
Illingworth & Kay (366)	0–3 yr.	6	4	..	2 (33%)	4 (67%)
Grimson et al. (266)	13 mo.–4 yr.	36	3‡	11§	23¶ (64%)	13 (36%)
Total	..	292	..	..	224 (76.7%)	68 (23.3%)

* All but eight vagotomy alone.

† See vagotomy for peptic ulcer, Table 195.

‡ One GU developed without symptoms, healed spontaneously, and was termed a satisfactory result.

§ Six with mild, ulcerlike symptoms.

¶ All required subsequent operation.

Of 266 where information was given, 29, or 10.9 per cent, developed recurrences.

Of 260 where information was given, 30, or 11.5 per cent, developed severe and persistent gastric retention or diarrhea.

not provided in most of the reports. Recurrences occurred in 10.9 per cent of 266 patients. Persistent gastric retention, diarrhea, or a secondary drainage operation was reported in 11.5 per cent of 260 patients.

Vagotomy combined with gastroenterostomy or pyloroplasty for duodenal ulcer yielded satisfactory results in 90 per cent of 259 patients who were followed for from zero to four years (Table 193). Recurrences occurred in 3.8 per cent and persistent gastric retention or diarrhea occurred in 4.9 per cent of 184 patients.

In another group of 112 patients with duodenal ulcer, vagotomy was performed, but gastroenterostomy was added only when pyloric stenosis appeared to be likely. The period of follow-up ranged from zero to five years and 85 per cent experienced satisfactory results (Table 194).

Many surgeons agree that vagotomy is not indicated in gastric ulcer

Table 193

VAGOTOMY FOR DUODENAL ULCER (VAGOTOMY WITH GASTROENTEROSTOMY OR PYLOROPLASTY)

Author	*Duration of Follow-up*	*No. Cases Followed*	*No. Recurrences*	*No. Severe and Persistent Motility Disturbances*	*Satisfactory*	*Unsatisfactory*
Collins et al. (376)	5–18 mo.	83	4	4	74 (89%)	9 (11%)
Colp (216)	6–24 mo.	20	2	0	18 (90%)	2 (10%)
Walters et al. (203)	0–3 yr.	75	..*	..	67 (89%)	8 (11%)
Miller & Olwin (210)	0–2 yr.	52	1	5	46 (88%)	6 (12%)
Grimson et al. (266)	13 mo.–4 yr.	29	0	0	29 (100%)	0 (0%)
Total	..	259	..	..	234 (90.3%)	25 (9.7%)

* See vagotomy for peptic ulcer, Table 196.

Of 184 where information was given, seven, or 3.8 per cent, developed recurrences.

Of 184 where information was given, nine, or 4.9 per cent, developed severe and persistent gastric retention or diarrhea.

because of the danger of the ulcer being malignant. Also, the results of experiments on rabbits and dogs suggest that vagotomy may predispose to gastric ulcer in man. Several cases of recurrent gastric ulcer after vagotomy have been reported when the original ulcer was duodenal (214, 373). It has been suggested that vagotomy be performed in patients with a high-lying gastric ulcer and if the ulcer does not heal well then a gastric resection should be performed. In any case, we believe intensive medical therapy should be employed and a gastric resection done if the ulcer fails to heal well.

Vagotomy for gastric ulcer has been reported to have been done in

Table 194

VAGOTOMY ALONE, OR COMBINED WITH GASTROENTEROSTOMY WHEN CONSIDERED NECESSARY

Author	*Duration of Follow-up*	*No. Cases Followed*	*No. Recurrences*	*No. Severe and Persistent Motility Disturbances*	*Result*	
					Satisfactory	*Unsatisfactory*
Dragstedt & Camp (373)	1–5 yr.	88	4	5	76 (86%)	12 (14%)
Patey (268)	0–2½ yr.	24*	5	..	19 (80%)	5 (20%)
Total	..	112	9 (8%)	..	95 (85%)	17 (15%)

* Some with duodenopylorectomy.

19 patients, who were followed for from zero to 33 months. Satisfactory results occurred in 68 per cent of the patients (203, 210, 266).

Some authors have reported results on a group of patients on whom vagotomy, with or without a drainage operation, has been done for duodenal, gastric, and anastomotic ulcer, the period of follow-up being zero to three years. Satisfactory results were obtained in 87 per cent of 206 patients. Recurrences occurred in 13.5 per cent of 155 patients (Table 195).

Table 195

VAGOTOMY FOR PEPTIC ULCER

Author	*Duration of Follow-up*	*No. Cases Followed*	*No. Recurrences*	*No. Motility*	*Results*	
					No. Satisfactory	*No. Unsatisfactory*
Orr & Johnson (214)	3 yr.	6	..	..	6	0
	2–3 yr.	17	..	..	12	5
	1–2 yr.	22	..	..	20	2
	3 mo.–1 yr.	51	..	..	49	2
Total	3 mo.–3 yr.	96	..	..	87	9
Cameron et al. (212)	1–24 mo.	44	3	8	36	8
Harkins (380)*	..	*Vagotomy Alone*				
		20			15	5
		Vagotomy plus Gastroenterostomy				
		12	..	..	12	0
Meyer, Rosi & Stein (223)	6–15 mo.	34	4	..	30	4
Walters et al. (203)†	0–3 yr.	77	14	..	..	..
Total	..	206	..	..	180 (87.4%)	26 (12.6%)

* Includes Johns and Grace cases, with resection omitted.

† Not included in total. Number and per cent satisfactory results under duodenal and anastomotic ulcer.

Of 155 where information was given, 21, or 13.5 per cent, had recurrences.

For vagotomy for anastomotic ulcer, see page 1024.

FACTORS AFFECTING RESULTS OF VAGOTOMY. The insulin test (382) is used most widely to determine whether a complete vagotomy has been performed. This has been frequently supplemented, as it should be, by a

study of basal secretion. The ability of the stomach to secrete neutral red (383) has been suggested but does not have the merit of the other procedures mentioned, in our opinion.

The use of the insulin test is based on the fact that complete vagotomy in the dog prevents insulin-induced hypoglycemia from stimulating gastric secretion and motility. All the vagal fibers must be sectioned to abolish completely the response to insulin hypoglycemia. The response is said to be positive, indicating all fibers have not been sectioned, when an increase in acid concentration of 15 units occurs. A single negative response cannot be taken as conclusive proof of a complete vagotomy because the response to insulin may become positive months after the operation or any one negative test may be technically faulty. The basal or interdigestive secretion of acid is reduced after complete vagotomy, but the same may be true temporarily after an incomplete vagotomy. Since the excretion of neutral red depends on the rate of basal secretion, it adds no information of significance.

It is reported that complete vagotomy is effective in preventing recurrences, whereas incomplete vagotomy is not. As regards gastric retention and diarrhea, the impression is gained from the literature that they occur as frequently after incomplete as complete vagotomy. In 1947, Harper and Dragstedt (367) reported no recurrences in 142 complete and five recurrences in 18 incomplete vagotomies. At a later date, however, Dragstedt and Camp (373) reported a postvagotomy gastric ulcer in a patient with a negative insulin test. The results reported in the literature on this subject are shown in Table 196. While the follow-up period is too short to warrant a definite conclusion, it seems clear that recurrences occur more frequently in patients with an incomplete vagotomy. *If this observation continues to be confirmed, it will prove unequivocally that vagotomy has a favorable effect in preventing recurrences.* It does not follow, however, that it is the surgical therapy of first choice.

The vagotomy was incomplete in 21 per cent of 400 cases collected from the literature as compared to 11 per cent of 160 cases reported by Dragstedt et al. (Table 196). This, of course, is a disadvantage of the operation.

Transthoracic vs. Transabdominal Vagotomy. The results of these different approaches cannot be compared on the basis of the data available. It would seem probable that a more complete vagotomy may be done by the transthoracic approach. This approach has practically been given up because it insults the chest and heart, the ulcerating lesion cannot be inspected, a drainage operation cannot be done if needed, and the incidence of postoperative complications is higher than with the transabdominal approach.

Table 196

REPORTED CASES OF RECURRENCE OF AN ULCER AFTER COMPLETE AND INCOMPLETE VAGOTOMY

Author	Total Cases	Complete Vagotomy			Incomplete Vagotomy*		
		No. Cases Oper.	No. Cases Recurrent Ulcer	Per Cent Recurrent Ulcer	No. Cases Oper.	No. Cases Recurrent Ulcer	Per Cent Recurrent Ulcer
Harper & Dragstedt (367)	160	142	0	0	18	5	28
Meyer et al. (223)	30	22	0	0	8	4	50
Orr & Johnson (214)	69	69	2	3	..	..	..
Orr & Johnson (384)†	16	..	..	..	16	5	31
Colp (216)	18	12	2	17	6	1	16
Cameron et al. (212)	15	5	1	20	10	1	10
Walters et al. (203)‡	..	..	..	..	..	..	..
Total§	308	250	5	2	58	16	28

* Vagotomy was incomplete in 21 per cent of 400 cases reported in the articles cited.

† From two separate reports of 115 cases, 88 believed to be complete and 27 incomplete.

‡ Unsatisfactory results in 14 (30 per cent) of 46 cases with complete and four cases with incomplete vagotomy.

§ Recurrences in approximately 11 per cent of 308 patients.

Selection of Patients. Patients have usually been selected for vagotomy on the same basis as in the case of gastric resection. Although the literature provides no data on the results of vagotomy in relation to the reason for operation, *one is impressed by the lack of reports on bleeding after vagotomy, even when the operation was done for a bleeding ulcer.*

CAUSE AND TREATMENT OF UNSATISFACTORY RESULTS FOLLOWING VAGOTOMY. *Recurrences.* The cause of the recurrences is the same as in the case of any recurrence, unless the recurrence takes the form of a gastric ulcer, where the cause is chiefly due to retention and rough food. Although the true recurrence rate after vagotomy is uncertain at the present time, it seems evident that the recurrence rate is less when combined with gastroenterostomy than for vagotomy alone. It will be interesting to observe whether vagotomy will reduce the incidence of recurrences after gastroenterostomy. Vagotomy, by decreasing the secretion of acid, should decrease the recurrence rate, whereas gastric retention might tend to counteract this effect. It would seem, however, that vagotomy should decrease the incidence of anastomotic ulcer after simple gastroenterostomy.

The choice of treatment of recurrences following vagotomy depends to a large extent on the recurrence of symptoms. Some recurrences following the operation are mild and readily controlled with simple dietary measures (266, 368). This is in contrast to recurrences which appear after gastroenterostomy and gastric resection. In the case of incomplete vagotomy, Dragstedt (367) has reëxplored the lower end of the esophagus to section any fibers missed at the first operation. Others have employed a gastric resection. In fact, the patient is managed first as though vagotomy had never been done.

Disturbances of Motility. As stated above, disturbances of motility tend to disappear with time. The very early postoperative gastric distention and retention can best be managed by continuous gastric drainage through a nasal catheter. Later parasympathomimetic drugs, particularly urecholine, have been found to be particularly helpful (125, 134, 385, 387, 389). These drugs are helpful because the retention is due to loss of the tonic effect of the vagi. One must always keep in mind the possibility of mechanical obstruction, such as that of the duodenum by active or cicatrizing ulcers, or that of the stoma in cases with gastroenterostomy, or that in the efferent loop. Despite the use of urecholine, secondary operations may be necessary in some cases (134, 389).

The cause of the diarrhea appears to be a mystery because section of the vagi should remove their excitatory effect on the small intestine and leave the inhibitory effect of the splanchnic nerves unopposed. How this might cause diarrhea is inconceivable. However, if food stagnates in the stomach, particularly in the absence of acid, or in the loops of the intestine, irritating substances may be produced and cause diarrhea. If this is correct, then the administration of urecholine, by facilitating gastric evacuation, should prevent the diarrhea. Stein (318) observed this to be true.

Otherwise, the management of the diarrhea is similar to that of a dumping stomach, keeping in mind the fact that milk frequently predisposes to diarrhea and special food intolerances exist.

Weight and Anemia Following Vagotomy. Johnson (391) has reported that the postoperative weight of vagotomized patients tends to increase, in contrast to gastric resection, although some patients with postoperative motility disturbances lose considerable weight. No studies have been reported on the incidence of anemia following vagotomy, but it is suspected that vagotomy does not predispose to changes in the hemoglobin level of the blood, except in the presence of persistent diarrhea.

Results of Fundusectomy and Vascular Ligation

Fundusectomy may be performed by removal of a wedge-shaped segment of the greater curvature, tubular resection of the greater curvature,

or sleeve resection without a gastrojejunostomy. The results have been less satisfactory than gastric resection, in which the antrum is also resected. For instance, Connell (293) has recently reported the late results of fundusectomy in 25 patients. Six, or 24 per cent, had unsatisfactory results, largely because of recurrences.

Only one adequate follow-up of the results of vascular ligation for peptic ulcer has been reported. Wood (119) found that a jejunal ulcer developed within four years in three of 29 patients (10 per cent treated by vascular ligation and gastroenterostomy). This is the same as the incidence of postoperative ulcer after simple gastroenterostomy. While Somervell (88) has reported favorably on the results of vascular ligation, his follow-up is inadequate to draw conclusions. Because of the conditions under which he works, every patient with peptic ulcer is treated surgically. Therefore, the results he obtains are not comparable with those obtained when the operation is used on patients with intractable ulcers. Dodd (235) tried vascular ligation in a few patients and abandoned it because of unsatisfactory results. Hey (89), who quadruply ligates the vessels to prevent sympathetic regeneration, believes the results to be better than those of simple gastrojejunostomy, but not as good as those of gastric resection.

Diet after Gastric Operations

We believe the surgeon errs if he tells the patient before or after a surgical procedure for peptic ulcer that he should eat, drink, and live anyway he chooses. To so inform a patient is to invite either a recurrence of an ulcer or other digestive complaints. Since the design of the alimentary tract is physiologically reasonable and the stomach has functions, it is not reasonable to believe that the normal design can be distorted and the stomach resected without placing a strain on the factors of safety in the digestive apparatus. Why strain the diminished factor of safety by permitting the patient to return to an unhygienic mode of living and eating?

The diet should not be restricted as regards the choice of wholesome foods and drinks, with the possible exception of the first few months after operation. Five or six small meals during the day may be useful in preventing postprandial distress, and more than an average quantity of calories, protein, vitamins, and minerals may be required to prevent weight loss and nutritional deficiencies. The thorough mastication of food is a habit that is not difficult to acquire. If the patient will not acquire this habit, ground food should be prescribed; it can be made acceptable and appetizing, and is readily selected from any menu and prepared at home. A snack between meals and before retiring is easily provided and is just as pleasant a way to feed as the usual three meals. Some form of

ecreation, seven or eight hours of sleep, and abstinence from smoking nd drinking and caffeinated beverages constitute wise instruction to veryone. It is good advice even for the person with the so-called "cast-ron" stomach, who, as we all know, is subject occasionally to dietary lyspepsia.

Reporting Late Results

One of the difficulties in evaluating the late results of the surgical and medical treatment of peptic ulcer is the failure of authors to provide relatively precise data. Another difficulty is the lack of a standard and accurate method of reporting the late results.

For surgical procedures, the late results should be classified into the number of patients symptom-free, the number with trivial symptoms, the number who are improved but still not well, and the number who have developed recurrences or are no better or worse than before operation because of other complications. Those who are symptom-free and those with trivial symptoms have a satisfactory result. While such a classification is arbitrary, most patients readily fall into one of these categories (145).

It is frequently not possible to compare the late results reported in various articles. One author will record as the late result the condition of the patient at the time of his analysis, regardless of the previous course or the necessity for treatment in the follow-up period. Another author will record as the late result the poorest condition of the patient at any time in the follow-up period, assuming that a patient who has trouble at any time should be permanently dropped from the satisfactory group. Both considerations are important and should be recorded. That is, not only the poorest condition of the patient at any time should be recorded, but also his symptomatic condition at yearly intervals.

Since ulcers may recur 20, 30, or more years after treatment, it is impossible to determine the *end* result of any medical or surgical procedure. Only *late* results may be determined. In reporting late results, the duration of follow-up is exceedingly important. In analyzing the late results of the surgical treatment of peptic ulcer, we have, of necessity, used follow-ups such as "these patients were followed 2 to 10 years" or "these patients were followed for an average of 7.1 years." As will be pointed out below, a more accurate picture of the late results can be attained by using other methods. When the duration of follow-up covers some period such as "6 months to 10 years," the report is of limited value unless there has been an adequate *minimum* duration of follow-up for *all* patients. For instance, in evaluating the results of gastroenterostomy, the symptoms of the patient immediately after operation tell us nothing of the late results. However, 60 or 70 per cent of the recurrences will have manifested themselves within two years

of the operation, so that a rough estimate of the late results can be ma
if a *minimum* follow-up of two years is used in evaluating gastroenterost
Even then about 30 per cent of the recurrences will not have appea
so that the results appear better than they will eventually be.

Table 187

YEAR BY YEAR PROGRESS AFTER PERFORATION

Year of Follow-up	*First*	*Second*	*Third*	*Fourth*	*F*
Continuously symptom-free	392	254	160	107	
Mild symptoms at some time during follow-up	110	147	140	97	
Severe symptoms at some time during follow-up	99	151	157	136	
Total cases	596	552	457	340	1

A year-to-year follow-up of patients gives a much more illumina
view of the late results. Several variations of a year-to-year follow
have been suggested (145, 393-395). The year-to-year follow-up
may be illustrated by the following example. One hundred patients

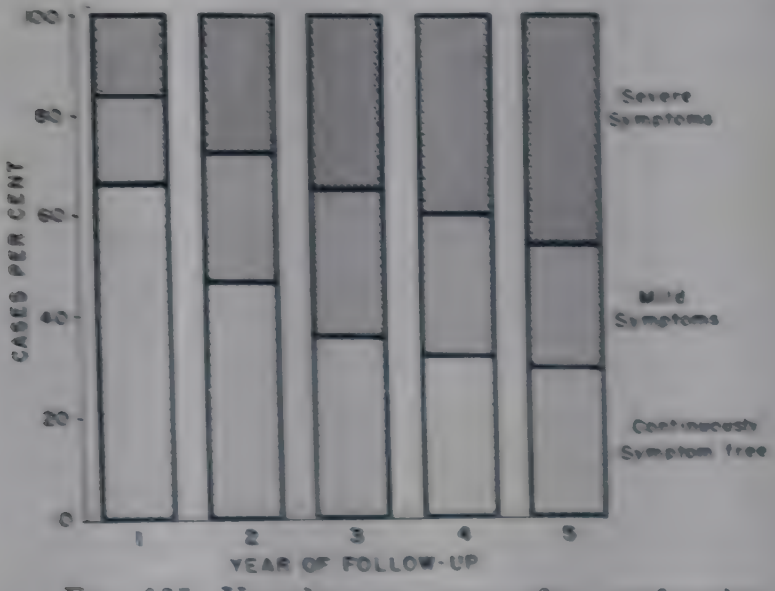


FIG. 135. Year-by-year state after perforation showing the proportion of patients with no symptoms or with mild or severe symptoms at any time in the follow-up period. (Ref. 394.)

operated upon, with three operative deaths. Of the survivors, 90 could
followed for one year. Considering the poorest condition at any time s
operation, 80 had satisfactory results. At the end of two years, 87 w

lowed, of whom 65 had satisfactory results. At the end of three 72 were still followed, of whom 57 had satisfactory results, etc.

Table 198

E BY YEAR STATE AFTER PERFORATION SHOWING SYMPTOMS DURING THE CURRENT YEAR OR RELAPSES

Year of Follow-up	First	Second	Third	Fourth	Fifth
ptoms	392	277	191	144	76
ymptoms	110	149	150	107	45
symptoms	94	126	116	89	45
l cases	596	552	457	340	166

ost of the features suggested here have been used by Illingworth et al. in studying the aftermath of perforated peptic ulcer. His tables and s which follow will serve to illustrate this method in practice.

able 197 shows the number of patients who remained continuously om-free and those with mild symptoms at any time in the entire -up period. In Fig. 135, the results of the study of the year by year ts after perforation shown in Table 197 are graphically represented.

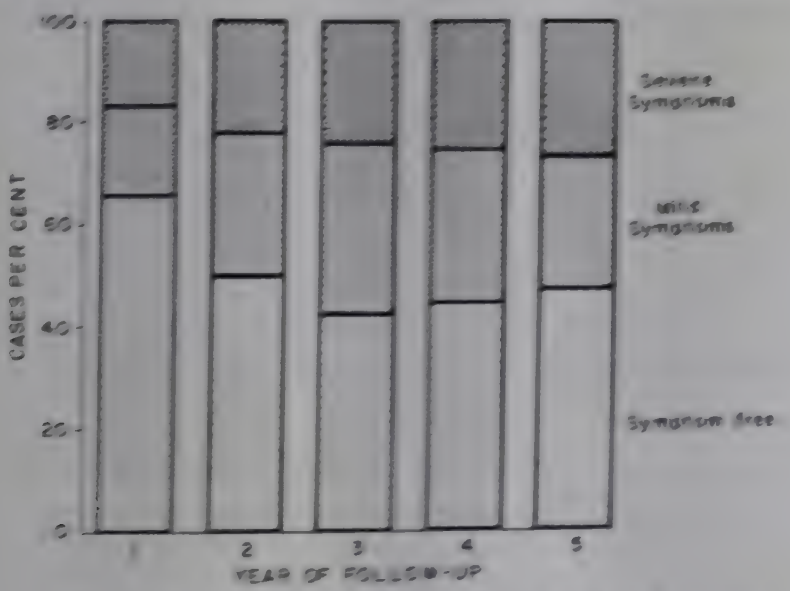


FIG. 136. Year-by-year state after perforation showing the proportion of patients symptom free in the current year and those with mild or severe symptoms *in the current year.* (Ref. 394.)

Table 198, Illingworth et al. recorded for each postperforative year umber of patients who *during that year* remained symptom-free or ed mild relapses. In Fig. 136, the year by year state after perforation

is graphically represented, showing the proportion of patients sympt
free *in the current year* and the proportion of patients with mild indiges
in the current year.

We strongly urge that this or some similar method of evaluating
treatment of peptic ulcer, and of other diseases as well, be adopte
evaluating late results.

Treatment of Perforated Peptic Ulcer

Introduction

The urgent and life-saving objectives of the treatment of perfor
peptic ulcer are (1) to stop the leakage and (2) to treat the perito
Some have added an attempt to cure the ulcer surgically to these
objectives.

The first attempt at simple closure of a perforated ulcer was prob
made in 1880 by Mikulicz (cited by DeBakey (396)). Prior to that
the therapy was symptomatic and the mortality was almost 100 per
in major acute perforation. With the adoption of active treatment, as
result of the introduction of aseptic surgery, lives undoubtedly bega
be saved but the mortality remained relatively high. Though the mort
has markedly decreased, a major acute perforation represents a ser
threat to life even today.

Mortality

The reduction in mortality as reported from clinics throughout
world since 1900 has been striking. Speck (397) and Graves (399),
reviewed the mortality statistics in German clinics, and Bager (398),
reviewed Swedish statistics, found a reduction of from approxima
58 per cent for the period of 1900 to 1910 to 28 per cent for the perio
1921 to 1931. At the Massachusetts General Hospital in Boston,
mortality was reduced from approximately 44 per cent up to 1916 t
per cent up to 1940.

The reduction of the mortality between the years 1930 and 1940
relatively slight, according to the way the data were presented by
Bakey in his large review (396). The way he arranged the data,
mortality of a group of 2140 collected cases reported in 1930 was 26.1
cent, and for 2746 cases in 1939 was 23.7 per cent.

The data we have collected have been arranged according to
period during which the perforation occurred, rather than according
the year the report was published. Some authors have reported the yea
mortality rate of perforated peptic ulcer. Their mortality rates, assemb
in Table 199, indicate that the mortality rate has decreased from 22
cent in 1937 to 9.3 per cent in 1944.

Table 109

Decrease in Yearly Mortality Rate of Perforated Ulcer

Author	1937		1938		1939		1940		1941		1942		1943		1944	
	No. Cases	No. and % Died	No. Cases	No. and % Died	No. Cases	No. and % Died	No. Cases	No. and % Died	No. Cases	No. and % Died	No. Cases	No. and % Died	No. Cases	No. and % Died	No. Cases	No. and % Died
Laer (261)*			24	10 (41.7%)	57	11 (29.7%)	68	5 (17.9%)	48	5 (13.2%)	57	1 (18.1%)	53	3 (9.7%)	75	8 (10.6%)
Illingworth et al. (409)†	674	81 (24.7%)	431	93 (21.6%)	443	75 (17.4%)	518	93 (18.0%)	614	113 (18.3%)	566	80 (14.1%)	578	83 (14.0%)		
Hushfield et al. (83)*	44	9 (20.0%)	49	12 (24.5%)	46	7 (14.0%)	49	8 (16.3%)	53	7 (14.0%)	59	5 (8.7%)	48	9 (18.0%)	49	8 (16.3%)
Olson & Nougue (328)*			22	3 (13.5%)	23	10 (43.5%)	16	3 (18.9%)	13	5 (41.7%)	17	2 (5.9%)	25	2 (8.0%)	23	4 (17.4%)
Houston (94)*					199	26 (13.1%)	221	33 (14.1%)	242	58 (23.5%)	190	24 (13.1%)	230	23 (10.2%)	209	12 (5.7%)
Total	407	90 (22.0%)	526	118 (22.4%)	737	129 (17.5%)	842	142 (17.1%)	969	188 (18.8%)	643	97 (15.1%)	970	88 (11.0%)	805	38 (5.1%)

* Operated cases only.

† Operated and nonoperated cases not segregated; includes all cases.

Table 200

DECREASE IN MORTALITY OF PERFORATED ULCER IN FOUR YEAR PERIODS FROM 1928 TO 1946

*Median Year of Period Covered by Report**	*No. Cases†*	*No. Deaths*	*Mortality Rate (Per Cent)*	*Range of Mortality (Per Cent)*
1928–1934‡	7753	1742	22.5	7.7 (418) to 53.0 (404
1935–1938§	2963	614	20.7	8.7 (335) to 33.3 (408
1939–1942¶	4930	777	15.8	3.6 (249) to 27.9 (328
1943–1946‖	1702	179	10.5	1.1 (248) to 18.1 (483

* Example: period covered by report, 1935 to 1945, median year, 1940.

† Operative mortality when given; otherwise both operated and nonoperated case

‡ References 71, 170, 278, 302, 304, 400, 401, 403–413, 418.

§ References 83, 166, 181, 228, 238, 306, 308, 323, 330, 352, 347, 372, 377, 37 409, 414–417.

¶ References 42, 83, 93, 133, 156, 164, 199, 239, 249, 267, 274, 307, 328, 353, 35 377, 409.

‖ References 62, 83, 93, 190, 240, 248, 267, 323, 328, 369, 372, 377, 409.

In Table 200, the mortality rates provided in articles which hav appeared since 1937 have been assembled. In doing this, the median ye of the period of years during which the cases of perforation occurred w determined; for example, if the report covers the years 1936 to 1944, th median year is 1940. Then, the number of perforations and deaths fo each median year was calculated, and the results for each median ye added for the periods shown in the table. This method of presentin practically all of the data in the literature shows that the mortality ra decreased from 22.5 per cent in 1928 to 1934 to 10.5 per cent in 1943 t 1946. It should be noted that the major portion of the decrease h occurred since 1938.

The most convincing way to demonstrate the decreasing mortality o patients treated for perforated ulcer is to compare the mortality from th same clinic or author before and after 1940. In each instance the mortali has been markedly reduced (Table 201).

SIGNIFICANT FACTORS INFLUENCING PROGNOSIS AND MORTALITY

In order to evaluate the factor or factors responsible for this mo recent decrease in mortality, the significant factors influencing prognos and mortality must be examined. The age and sex of the patient, the si of the lesion, and the duration of time elapsed between perforation an the institution of treatment are important and well recognized factor The type of procedure to be employed and the type of anesthetic to b

Table 201

REDUCTION IN MORTALITY OF PERFORATED PEPTIC ULCERS FROM INDIVIDUAL CLINICS

Author	Series Before 1940			Series After 1940		
	Period Covered	No. Cases	Per Cent Died	Period Covered	No. Cases	Per Cent Died
Kinnon (468)	1929–1940	112	29 5	1941–1946	64	7 8
z et al. (323)	1930–1940	52	28 8	1940–1946	43	9 3
ster (62, 419)	1935–1939	100	23 0	1940–1947	103	3 9
nfield et al. (83)	1937–1939	128	21 9	1940–1944	254	14 6
ns (372)	1936–1941	13	23 1	1942–1947	23	13 0
mpson & Prout (202)	1921–1934	424	28 7	1943–1945	100	15 0
(267)	1938–1939	61	34 4	1940–1948	257	14 4
Chinney & Holzer (377)	1935–1940	131	19 9	1941–1946	168	11 3
s & Norgore (328)	1938–1939	45	29 1	1940–1944	93	16 1

d are controversial but undoubtedly influence the mortality rate. ally, new concepts and new drugs have been introduced which have pletely altered pre- and postoperative care.

AGE OF PATIENT. With increasing age, the risk of perforation becomes ater. In cases reported from 1930 to 1939 which were collected by Bakey (306), the mortality rate was 14.3 per cent in patients aged from 19, 12.2 per cent from 20 to 29, 18.9 per cent from 30 to 39, 28.0 per t from 40 to 49, 40.8 per cent from 50 to 59, 55.3 per cent from 60 to and 53.8 per cent from 70 to 79.

Table 202 will indicate that a change in the age incidence of per- ted peptic ulcers is not responsible for the lessened mortality because age incidence since 1940 is almost identical with that occurring before 0.

SEX OF PATIENT. Perforation in the female carries a worse prognosis n in the male. Thus, in DeBakey's collected series, the mortality was per cent in 2152 males and 43.9 per cent in 474 females. In a particu- large series from the West of Scotland (409), the mortality rate for 6 males was 18.6 per cent and for 360 females it was 36.4 per cent. In cases occurring since 1940 (93, 202, 248, 359), 93.9 per cent of the ents have been males. In DeBakey's series, 92.2 per cent were males. decreased mortality rate since 1940 cannot be accounted for on the s of a change in the sex incidence of perforation.

SITE OF LESION. Although a few observers (340, 357, 418) have noted gher mortality in perforated duodenal than in perforated gastric

Table 202

AGE INCIDENCE OF PERFORATED PEPTIC ULCER

Age Range	*Collected Series, Cases Occurring 1940 and After (190, 202, 248, 249, 359)*		*Collected Series, Cases Occurring 1939 and Before (396)*	
	No.	*Per Cent*	*No.*	*Per Cent*
0–20	11	2.2	258	3.8
20–30	103	20.8	1645	23.9
30–40	128	25.9	1893	27.4
40–50	117	23.6	1532	22.4
50–60	87	17.6	1032	15.0
60–70	36	7.3	398	5.8
Over 70	13	2.6	117	1.7
Total	495	100.0	6875	100.0

ulcers, the majority have found that the risk is greater with gastric ulcers. DeBakey's collected series indicated that the mortality rate for 1389 gastric ulcers was 33.3 per cent; for 3152 duodenal ulcers, 21.1 per cent; and for 284 pyloric ulcers, 22.2 per cent. Houston (93) found that 16.7 per cent of 1100 patients with perforated duodenal ulcers died, and 20.8 per cent of 125 patients with perforated gastric ulcers. Illingworth, Scott, and Jamieson (409) found that the mortality rate of 3220 perforated duodenal ulcers was 15.2 per cent and for 583 perforated gastric ulcers it was 40.3 per cent.

The increasing incidence of perforated duodenal ulcers (p. 544) is evident even in those cases which have occurred since 1940. Thus, 81.2 per cent of 1544 perforations were from duodenal ulcers (Table 203). In

Table 203

SITE OF PERFORATED PEPTIC ULCERS

Site	*Collected Series, Cases Occurring 1940 and After (93, 190, 202, 248, 249, 359, 369)*		*Collected Series, Cases Occurring 1939 and Before (396)*	
	No.	*Per Cent*	*No.*	*Per Cent*
Duodenal	1254	81.2	5791	51.2
Gastric	265	17.2	4400	38.9
Pyloric	25	1.6	1114	9.9
Total	1544	100.0	11305	100.0

11,305 collected cases (396) occurring before 1940, only 51.2 per cent were said to be duodenal. Since the mortality of perforated duodenal ulcer is less than for gastric ulcer (p. 1050), the relative increase in the number of perforated duodenal ulcers reported in the literature may account in part for the decreased mortality rate of perforated peptic ulcer since 1940.

Time Elapsing between Perforation and Treatment. This is one of the most significant factors in the prognosis of perforated gastroduodenal ulcer. In DeBakey's collected series, the mortality was 10.5 per cent in the first six hours, 21.4 per cent from six to 12 hours, 38.5 per cent from 12 to 18 hours, 62.4 per cent from 18 to 24 hours, and 61.5 per cent over 24 hours.

The time factor is not necessarily the most important nor is the prognosis necessarily commensurate with the delay interval (337, 412). Some authors (337, 401) have found the operative mortality to be less for perforated ulcer where a day or two has elapsed than where 18 or 24 hours have elapsed. A perforation that has occurred 48 hours previous to operation may become walled off or plugged by adhesions soon after the occurrence of the perforation, resulting in a relatively small amount of peritoneal contamination. Obviously, such a patient is less likely to develop a generalized peritonitis than one whose perforation has remained open, even though he is operated upon within 12 to 24 hours after the perforation.

In a small collected series of 457 cases (Table 204) occurring in 1940 and after, 77.7 per cent were operated upon within six hours after the perforation. In DeBakey's collected series of 7685 cases occurring before 1940, 73.5 per cent were operated upon within six hours of the perforation. The improved mortality rates since 1940 cannot be accounted for by more prompt treatment, since *there has been a decreased mortality rate for all periods of time elapsing after perforation* (Table 204).

Peritonitis and a decline in the general condition of the patient are responsible for the increased mortality when many hours are allowed to elapse before treatment is begun. It is generally agreed that the peritonitis which occurs in the early postperforative period is primarily chemical and the result of peritoneal soiling with gastric and duodenal contents and secretions. Subsequently, a more serious bacterial peritonitis develops.

The inhibitory effect of acid gastric secretion on bacterial growth is well known (68, 257, 319, 344). However, secretion of hydrochloric acid ceases following perforation (118, 151), and the sterilizing effect of gastric juice disappears. This is presumably related to the development of bacterial peritonitis in that nonsterile gastrointestinal contents are then spilled into the peritoneal cavity.

Table 204

RELATIONSHIP OF MORTALITY TO TIME ELAPSING FROM PERFORATION TO INSTITUTION OF TREATMENT

Duration of Time from Perforation	*Total No. of Cases*	*Per Cent of Total Cases*	*No. Died*	*Per Cent Died*
Collected Series Occurring 1940 and After (190, 202, 248, 359, 369)				
0–6 hr	165	77.7	7	4.2
6–12 hr	190		13	6.8
			20	5.6*
12–24 hr	67	14.7	12	17.9
Over 24 hr	35	7.6	11	31.4
Total	457	100.0	43	9.4
Collected Series Occurring Before 1940 (396)				
0–12 hr	5648	73.5	826	14.6
12–24 hr	1231	16.0	525	42.6
Over 24 hr	806	10.5	496	61.5
Total	7685	100.0	1847	24.0

* McElhinney and Holzer also reported a decrease in mortality to 6.4 per cent in cases operated upon in the first 12 hours from 1944 to 1947. From 1935 to 1941, they reported that the mortality rate in the first 12 hours was "substantially the same as DeBakey's."

Most reports indicate that positive cultures can be obtained from the peritoneal cavity within 12 hours of perforation in approximately one half the patients. After 12 hours, the culture is positive in approximately 80 per cent of patients (118, 267, 375, 381). Within six hours, the incidence of a positive culture ranges from 8 to 62 per cent (42, 118).

The unfavorable prognostic significance of a positive culture is shown (Table 205) by the observation that 33.6 per cent of 217 patients with a positive culture and only 8.0 per cent of 187 patients with a negative culture died (118, 267, 306, 379, 408).

Since positive cultures can be obtained with increasing frequency as time is allowed to elapse from perforation to the institution of treatment, and since a high mortality rate occurs in the presence of a positive culture, it is evident that the mortality rate should increase as greater periods of time are allowed to elapse between perforation and treatment.

Dehydration, electrolyte imbalance, and circulatory collapse will be seen frequently in patients who have perforated and have not been treated for many hours. Grahame (259) felt that these factors were of greater

portance than bacterial contamination of the peritoneum. However, bulk of the evidence seems to indicate that the greater mortality of cases is related to bacterial infection and that other phenomena are ndary. Nevertheless, Graham showed that the mortality rate would lowered by adequate preoperative care to combat dehydration and ulatory disturbances.

Table 205

RELATIONSHIP OF POSITIVE BACTERIAL CULTURES TO MORTALITY

Author	Positive Culture			Negative Culture		
	No. Cases	No. Died	Per Cent Died	No. Cases	No. Died	Per Cent Died
wold & Associates (379)	22	9	40.9	31	3	9.7
son (306)	10	7	70.0	21	0	0.0
cKinnon (408)	26	10	38.6	15	0	0.0
son et al. (118)	18	12	66.7	16	4	25.0
er (267)	141	35	24.8	104	8	7.7
Total	217	73	33.6	187	15	8.0

PRE- AND POSTOPERATIVE CARE. It may be concluded that the recent crease in the mortality rate of perforated peptic ulcer is not dependent, any marked degree, on differences in the sex or age of the patient, in the e of the lesion, or in time of initiating treatment. *The mortality rate has n decreased for all ages, both sexes, gastric and duodenal lesions, and all periods er perforation.*

The major factor in the reduction of the mortality rate has been the olication of recent advances in pre- and postoperative care. The general of intravenous fluids did not occur until the early 1930's. A better derstanding of body fluid and electrolyte balance evolved. Also, in ent years, venous thrombosis and pulmonary embolism have been ognized earlier and treated more effectively.

In 1935, Marriott and Kekwick (327) devised a drip technic for tinuous administration of blood. Liberal quantities of blood and plasma e made available through blood banks from 1940 to 1942. The value blood and plasma transfusions in peritonitis is well known. Shock, as nifested by a low blood pressure, is not common in perforated ulcers, ause it has been found to occur in only from 6 to 7.4 per cent of patients 3, 354, 377). When shock is present, plasma or blood transfusions are nitely indicated.

Wangensteen (378) introduced continuous gastric suction in and within several years the procedure was adopted by all surgeons perforated ulcer, many pass a stomach tube before operation and al all employ continuous suction in the postoperative period. The valu gastric and duodenal decompression is demonstrated by the re obtained from nonoperative therapy of perforated ulcer by contin decompression of the stomach (p. 1061). Continuous suction is defin indicated in the patient too ill for operation or preoperatively in patient who may require a period of preparation before surgery.

CHEMOTHERAPY AND ANTIBIOTICS. Bacterial infection, primarily o peritoneal but also pulmonary, is the greatest cause of postoper complications and death in perforated peptic ulcer. The incidenc postoperative complications is undoubtedly related to the mortality This is shown by the following observations. DeBakey (370) studied incidence of various complications among 772 collected cases of c plicated perforated ulcers occurring before 1940; 32.8 per cent pulmonary complications; 24.7 per cent had contaminating perito 7.2 per cent had localized intraperitoneal abscesses; 25.4 per cent wound infections or evisceration; and 9.9 per cent had miscellan complications, including fistulas, ileus, hemorrhage, etc. On studying cause of death in 952 cases of fatal perforated ulcer occurring before 1 it was found that 53.2 per cent died of generalized peritonitis and 4 cent died of subphrenic abscess. Pulmonary affections were respons for 20.8 per cent of the deaths, and 22 per cent died of other ca including shock, cardiac conditions, hemorrhage, ileus, etc. Hirsh et al. (83) found that 70 per cent of 150 fatal cases of perforated u reported from 1940 to 1945 died of either intraperitoneal or pulmo infection. Furthermore, as was pointed out above (Table 208), mortality rate of patients with positive bacterial cultures was 33.6 cent and with negative cultures, only 8 per cent. Streptococci are the common organisms cultured from the peritoneal cavity and also the dangerous (118, 267, 379). *E. coli*, staphylococci, and diphtheroids also frequently found. Anaerobic bacteria do not usually appear 18 hours after perforation (118).

The clinical use of the sulfonamides became prevalent between 1 and 1943 and penicillin between 1945 and 1946. Streptomycin and antibiotics have become available more recently. Considering the portance of bacterial infection as a cause of death in perforated u these antibacterial agents seem largely responsible for the redu mortality of perforated ulcer.

In 503 cases reported in the literature in which sulfonamides alon in combination with penicillin were used, the mortality was only 7.5

1, 170, 202, 239, 240, 248, 307, 330, 369, 377, 402). While the local
e in the peritoneal cavity has been largely abandoned, their use
rated ulcer undoubtedly reduced the mortality (93, 170, 239, 307,
oth experimentally (133, 309, 329) and clinically (300), massive
l penicillin appear to be the most effective means of treating
tis. One hundred thousand or more units of penicillin should be
very three hours.

reduction in the incidence of wound infections has probably re-
. Too few observations have been reported to establish this point
2, 239, 240, 248, 369), since other factors may also be important,
the decreasing tendency to drain the abdomen in perforated
ulcer.

ainage or Abscesses. This is being used less and less. Some surgeons
handoned routine drainage and some use it only in late cases. This
to the development of much doubt regarding the value of drainage
eralized peritonitis. Some have even claimed that drainage is
ous. It is not possible to make a statistical evaluation of the effect
nage on mortality or complications, because drainage has usually
mployed in those cases where considerable peritoneal contamination
flammation exist. Both mortality and the incidence of complica-
367) increase with the time which elapses between perforation and
ent. Nevertheless, the mortality rate and incidence of complica-
to appear to be lower in similar cases when treated by primary
than when drains are employed (241, 402). Low mortalities have
eported when drainage was avoided (62, 248, 369), indicating that
ually unnecessary.

ile drainage in general peritonitis seems of little avail, its use in
ence of localized abscesses is indicated.

itoneal lavage is less vigorously employed than formerly. Some
e fluid only if obscuring the site of the ulcer (62, 343). Others (226)
ly aspirate the abdominal cavity, particularly the subhepatic

ice of Anesthesia. The choice of the anesthesia to be used during
on is controversial. DeBakey found that the mortality was 17 per
990 cases in which spinal anesthesia was used and 30 per cent in
which general anesthesia was used. However, some surgeons have
d low mortalities with general anesthesia or no difference in
y between general and spinal anesthesia (247, 377).

ice of Operation. In the United States, Canada, and England,
losure is held to be the best method of treating perforated peptic
However, many European surgeons have used gastric resection as
ation of choice. Both in this country and abroad, gastroenteros-

tomy or pyloroplasty have frequently been performed with simple c
or excision of the perforated ulcer.

The advocates of simple closure believe the best treatment f
dangerously ill patient with a perforated ulcer is the simplest and qu
procedure which will prevent further spilling of the peritoneal cavity
believe that a further operation, if necessary, can be done under
ideal circumstances at a later time.

Those who favor additional procedures maintain that the morta
no higher in selected patients and that the chances of cure are
higher. They furthermore believe that the danger of pyloric or duo
narrowing from the closure is eliminated.

In order to evaluate properly the various operative procedures
necessary to examine the mortality rate and late results of each.

Mortality Rates of Different Operations for Perforated Peptic Ulcer. In a study of the literature appearing before 1941, DeBakey (396) found the mortality rate of simple closure to be 25.3 per
for 3589 cases, of closure plus gastroenterostomy to be 20.4 per ce
3045 cases, of excision and pyloroplasty to be 15.9 per cent for 258
and of partial gastrectomy to be 13.4 per cent for 2502 cases. Wh
first glance, the mortality of the more radical procedures seems
than that of simple closure. DeBakey has pointed out that this ac
may not be so. Where radical procedures are performed for perfo
ulcers, only the early and more favorable cases are so treated and the
risk cases treated by simple closure. Not only does this raise the mor
rate of simple closure, but also makes the mortality rate of gastric res
for perforated ulcer seem more favorable than is actually the ca
seems hard to believe than the mortality of gastric resection is lower
that of simple closure.

The mortality rate of simple closure is now 10 per cent or less i
cases. Nevertheless, mortality rates of less than 5 per cent for gastric r
tion in selected cases of perforation have been published in recent
(71, 302, 388). On the basis of the present evidence, Bisgard (392), B
gaard (71), and others have concluded that gastric resection ma
performed in early and selected cases of perforated ulcer with a mort
rate which differs little from simple closure or from the mortality o
elective gastric resection.

Recurrence after Perforation. There is considerable diff
in evaluating the late results of operations for peptic ulcer. Va
methods of reporting late results appear in the literature. In ord
evaluate the late results, the various reports must be compared on a
mon basis. This means that the results reported by some authors m
reanalyzed and recorded in a somewhat different form. For perfo

shown these classifications: (a) symptom-free cases, (b) recurrences (in a few circumstances this includes unsatisfactory results other than recurrences), and (c) the number of all cases followed regardless of operation.

A peptic ulcer is a disease prone to recurrences and recurrences have always worse than immediate results, whether it be for medical treatment, anatomical operations, vagotomy, or perforation. For this reason no individual report is of value unless there has been an adequate period of follow-up. No collective study is of value when it includes individual reports with inadequate or short-term follow-up.

Table 20

RESULTS OF MEDICAL PERFORMANCE UPON PATIENTS WITH DUODENAL ULCER

Author	No. Cases Followed	Duration of Follow-up	No. Symptoms	Recurrences*	No. of All Cases Followed During Observation
Collected Series of Porter (MA)					
Porter, Collected Series	764	--	368 (50.8%) (range, 14–81%)	376 (49.2%) (range, 19–86%)	Of 324 cases, 96 (14.7%) re-operated (range, 10–46%)
Series Collected from Literature Since 1940					
Cooke & Cooper (304)	41	1–12 yr.	7 (17.1%)	34 (82.9%)	
Madden (274)	28	2 mo.–5 yr.	19 (67.9%)	9 (32.1%)	6 (21.4%)
Ivy & Schilling (307)	71	More than 1 yr.	23 (32.4%)	48 (67.6%)	21 (29.5%)
Hendricks (166)	57	6 mo.–11 yr.	13 (22.8%)	44 (77.2%)	17 (29.8%)
[illegible]	79	Less than 1 yr. to more than 5 yr.	32 (45.7%)	38 (54.3%)	10 (14.3%)
[illegible] et al. (394)†	457	5 yr.	164 (35.0%)	297 (65.0%)	65 (14.2%)
[illegible] (53)	211	11–14 yr.	77 (36.5%)	134 (63.5%)	45 (21.3%)
[illegible]ennett (335)	53	Average 6.5 yr.	3 (5.6%)	50 (94.4%)	8 (15.1%)
[illegible] (96)	18	7 mo.–9 yr.	6 (33.3%)	12 (66.7%)	6 (33.3%)
[illegible] (390)	100	3–19 yr.	28 (28.0%)	72 (72.0%)	14 (14.0%)
[illegible]	1100	[illegible]	[illegible] (11.1%) (range, 5 to 47.9%)	[illegible] (88.9%) (range, 10 to 94.4%)	Of 1062, cases [illegible] (10.2%) re-operated (range, 0.9 to 33.3%)

*Recurrence on the meaning of re-operation is not homogeneous for medical or operative. About 40 per cent recurrences are mild, about 20 per cent are severe, and about 30 per cent require further surgery. Mixed (near-by-year) follow up. There were [illegible] (See Fig. 107.)

Simple Closure. Parker (404) analyzed a collected series according to the method we have chosen, although the duration of follow-up in the various series was not recorded (Table 206). Of 764 cases followed after simple suture for acute perforation and reported prior to 1940, 50.8 per cent (range, 14 to 81 per cent) were symptom-free and 49.2 per cent (range, 19 to 86 per cent) had suffered a recurrence. Of 524 cases in which information regarding reoperation was given, 18.3 per cent (range, 10 to 44 per cent) required another operation for perforation or other complications. In 1106 cases followed and reported since 1940 (Table 206), 33.3 per cent (range, 5.6 to 67.9 per cent) were symptom-free and 66.7 per cent (range, 32.1 to 94.4 per cent) had recurrence of symptoms. Of 1065 cases where information regarding reoperation was given, 18.0 per cent (range, 13.5 to 33.3 per cent) required another operation. The literature on the severity of recurrences is too heterogeneous for statistical evaluation, but about 50 per cent of the recurrences are mild, about 25 per cent are severe but do not require operation, and about 25 per cent require further surgery (Table 207).

Table 207

SEVERITY OF RECURRENCES FOLLOWING SIMPLE CLOSURE

Author	*Duration of Follow-up*	*No.*	*Symptom-free*	*Mild or Moderate Recurrence*	*Severe Recurrence*	*Operated*
Kingsbury & Schilling (307)	>1 yr.	71	23	15	12	21
Moore & Hendricks (166)	6 mo.–11 yr.	57	13	21	6	17
Forty (199)	<1 yr.–5 yr.	70	32	24	4	10
Illingworth et al. (394)	3 yr.	457	160	140	92	65
Williams (390)	3–10 yr.	100	28	49	9	15
		755	256	249	123	128
Total	..	100%	33.9%	32.9%	16.3%	16.9%

Of 500 recurrences: 249 mild = 49.8 per cent, 123 severe = 24.6 per cent, 128 reoperated = 25.6.

In Parker's collected series, about one half of the patients remained symptom-free during the period of observation, while in the later series only one third remained symptom-free. We attribute the difference to selection of cases in the later series in which an adequate duration of follow-up occurred. Parker himself recognized that the number of recurrences increased with the duration of follow-up.

Many of the recurrences occur within one or two years (93, 199), but a significant number occur after two years (307). Illingworth, Scott, and Jamieson (394) reported 596 patients followed at yearly intervals for five years. At one year, 65.8 per cent had remained symptom-free. Of 166 which could be followed for five years, only 28.3 per cent remained symptom-free. Their yearly results are presented graphically in Fig. 137.

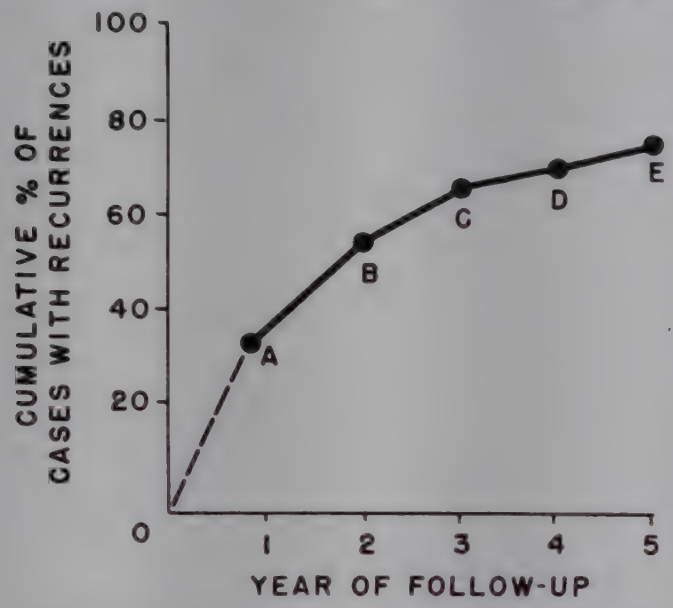


FIG. 137. Showing the yearly cumulative incidence of recurrences following simple closure of perforated peptic ulcer. (Modified from Illingworth, Scott and Jamieson (ref. 394)).

This graph of recurrences is nearly a perfect image of the cumulative incidence of recurrences of peptic ulcer following medical therapy (Fig. 132, Chapter 22). This is a particularly important phenomenon pertaining to peptic ulcer. *Perforation is merely an incident, an important incident, in the life of the patient, but his disease remains peptic ulcer, subject to remission and relapse.* Many have claimed that perforation cures the ulcer. No doubt, most patients are temporarily relieved of their symptoms as the result of a period of rest in the hospital and transient postoperative ulcer management. But they are subject to recurrences in a manner similar to other patients with peptic ulcer.

FACTORS WHICH AFFECT RECURRENCES AFTER PERFORATION AND SIMPLE CLOSURE. *Diet.* Dieting seems to have no decided influence on the incidence of recurrences. Adding the data of Houston (93) and Williams (390) together, 33.5 per cent of 101 cases who dieted for a variable period after perforation remained symptom-free, whereas 44.8 per cent of 178 cases who did not diet remained symptom-free. While the difference in these percentages is only on the borderline of significance ($\chi^2 = 3.4$), we believe that the patient should be maintained on medical management

following perforation, and that he should follow hygienic living as outlined in the section on recurrence following medical therapy.

Age. Age is a factor which definitely influences the rate of recurrence. When the data supplied by Forty (199) and by Illingworth et al. ([illegible]) are combined, a statistically significant difference is found. Of 415 patients less than 50 years of age, 33.4 per cent remained symptom-free, whereas 55.4 per cent of those above 50 years of age remained symptom-free following a simple closure for perforation; this comparison, however, is made without regard to the length of the period of follow-up.

Duration of Previous Ulcer History. The longer the duration of the previous ulcer history before the perforation, the greater the likelihood of a recurrence of symptoms (93, 199, 394). This is similar to peptic ulcer after medical therapy.

Late Results of Pyloroplasty or Gastroenterostomy Combined with Simple Closure for Perforated Peptic Ulcer. Drainage operations have been combined with simple closure in order simultaneously to treat the ulcer and to prevent gastric stasis from duodenal or pyloric narrowing. It is now generally agreed that simple suture rarely causes sufficient duodenal or pyloric narrowing to cause gastric stasis.

There are few well documented statistics regarding the late results of gastroenterostomy or pyloroplasty in perforated ulcer. In DeBakey's collected series of 764 cases of gastroenterostomy for perforated ulcer, 67 per cent were reported as being relieved of ulcer distress, 10.5 per cent as having slight distress, and 22.5 per cent as having severe recurrent symptoms. Parker (404) reported a collective series of 33 cases of perforated ulcer treated by excision and pyloroplasty, of which 70 per cent remained well. These figures are reported without regard to the duration of follow-up.

They indicate that these operations do not afford protection against recurrence of the ulcer. The figures compare with those reported for gastroenterostomy and pyloroplasty for nonperforating peptic ulcer. It is important to recall that anastomotic ulcers which recur after gastroenterostomy and simple closure of a perforated ulcer are particularly prone to perforate (264, 350, 402).

Late Results of Gastric Resection for Perforated Peptic Ulcer. In a series of 385 cases of gastric resection for perforated ulcer collected by DeBakey, 90.6 per cent had good or fair late results. One would not expect the late results to be better, since only slightly more than 90 per cent of the gastric resections for nonperforating ulcer produce satisfactory late results.

In conclusion, simple suture of perforated ulcer is the safest and

lest method of treating perforated ulcers. However, only one third in symptom-free, and about 18 per cent will require a subsequent ation. Gastroenterotomy or pyloroplasty in conjunction with simple ure are rarely indicated, since they increase the operative time and followed by relatively unsatisfactory results. Gastric resection can erformed with a low mortality in early and selected cases by skilful experienced gastric surgeons. Under such conditions, it should be idered in cases of perforation with concomitant hemorrhage, perfora- of ulcers associated with organic pyloric stenosis, perforation of stomotic ulcers which have followed gastroenterostomy (331), re- ing perforations, and in patients with a long and severe history of ic ulcer.

Nonoperative Treatment of Perforated Peptic Ulcer

Introduction. For many years, it was assumed that operation was ays indicated immediately in perforated peptic ulcer. This was based *priori* reasoning and on the evidence that the mortality rate for non- rated patients is higher than that for operated cases. For instance, the ative mortality in DeBakey's series was 23.4 per cent for 15,341 cases, the general mortality was 25.2 per cent for 16,752 cases. However, evidence does not consider the fact that operation is safer in the group atients seen late in whom there is evidence of spontaneous closure, he fact that patients too ill to operate safely are managed medically. example, McIlhinney and Holzer (377) reported 38 patients seen or more hours after perforation. Of 14 who were operated on, 71 per t died. Of 24 who were not operated on, 66 per cent died. Thompson) reported 76 patients seen from 1921 to 1934 who were not operated 75 of whom died.

Some surgeons have reported excellent results in patients seen late n treated by decompression or continuous gastric drainage without ation, as recommended by Wangensteen (13). Bartell (248) treated ically five cases who had been perforated for more than 12 hours and ecovered. Barber and Madden (274) reported observations on five nts in whom many hours had elapsed and there was evidence of taneous closure. All recovered on nonoperative therapy. Ullfelder and (330) have advised that selected cases be treated nonoperatively 12 hours have elapsed. The mortality was 47.5 per cent in a total of atients treated without operation by Olson and Norgore (328) and man (348), but the criteria for selection of cases were not stated. It tain that some patients when not operated upon survive an acute per- ion and it appears that some patients who are seen many hours after

perforation may best be treated without operation. This includes patie with evidence of spontaneous closure and patients too ill for operati However, more evidence is needed.

Elective Nonoperative Treatment of Early Perforation. In recent literature, several articles have appeared in which all perforati have been treated electively by nonoperative means. Taylor (38 reported that he repeatedly found the ulcer sealed off by adhesions or adjacent viscus at operation, and undertook nonoperative therapy this reason.

Essentials of Elective Nonoperative Treatment. The essentials of elect nonoperative treatment of perforated ulcer are (1) decompression of t stomach by continuous suction, (2) parenteral fluids, (3) large doses penicillin, and (4) enough morphine to allow the patient to breathe co fortably and prevent pulmonary complications.

Most of the authors avoid nonoperative therapy when there has been a re meal before perforation. This seems well advised in view of the experiment work of Bergh, Bowers, and Wangensteen (370). They found the mortali following experimental perforation of the empty and full stomach to 6.9 and 86.7 per cent respectively. They also found that when spontaneo closure was handicapped by the injection of a sclerosing solution into t stomach wall before perforation, the mortality of the fasting animals w increased to 40 per cent.

Results. The mortality rate of the elective nonoperative therapy perforated peptic ulcer in 138 cases is 8.0 per cent (range, 0.0 to 21.3 p cent) (Table 208). Unfortunately, the diagnosis of perforated peptic ulc has not been definitely established in most cases, although pneumoper toneum has been noted in a few.

Table 208

Elective Nonoperative Therapy of Perforated Peptic Ulcer

Author	*Period Covered*	*No. of Cases*	*Died*	*Per Cent Died*
Mullen (294)	–1942	28	3	10.7
Bedford-Turner (364)	1945	6	0	0.0
Taylor (386)	1945–1946	28	4	14.3
Visick (345)	1945–1946	14	3	21.3
McClintock (292)	–1947	35	1	2.9
Bingham (138)	–1948	5	0	0.0
Seeley et al. (253)	1945–1948	22	0	0.0
Total		138	11	8.0

...ile the mortality rate of this form of treatment is slightly lower than ...erative mortality since 1943 (i.e., 10.8 per cent), it should be emphasized that the method has not been thoroughly tested. Almost all surgeons ...se to operate on perforated peptic ulcer, and many have objected ...ctive nonoperative treatment. Many more cases must be observed ...he results compared with a paired series of operated cases.

Treatment of Hemorrhage

...he results of the surgical treatment of hemorrhage have been pre...t previously when the indications for surgery and the choice of the ...al procedure were discussed (p. 970), and when the treatment of the ...isfactory results of gastroenterostomy and gastric resection were ...dered (p. 1024).

Summary

...The more important observations made in this chapter will be summarized in Chapter 24.

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CHAPTER 24

Summary of Therapy

Medical Therapy

The aim of medical therapy is to stop the symptoms, heal the ulcer, and prevent recurrences.

Because acid-pepsin is corrosive and pepsin is only slightly active at the point where "free acidity" ceases to exist, namely, pH 3.5 to 4.0, "*adequate neutralization*" has been assumed to exist when the pH of the gastric contents ranges from 3.5 to 4.0. Some have assumed that neutralization of "free acidity" for a period of 12 hours during the day is adequate. Others believe that 24 hour neutralization is best, at least during the first few days of management, particularly with a penetrating or a bleeding ulcer.

For neutralization of the free acidity, a wide choice of alkalies is available. The disadvantage of alkalosis when absorbable alkalies are used may be avoided by the administration of adequate sodium chloride (10–15 Gm. daily) and water (4 to 6 l.), providing extensive renal disease is not present.

Frequent feedings of a liquid or soft diet of bland foods form a part of every diet used for peptic ulcer. Hourly feedings with a neutralizing agent given day and night orally or by continuous drip are indicated in the presence of a penetrating ulcer, of severe ulcer distress, or of manifest hemorrhage. The diet should obviously be high in high-quality protein, vitamins, and iron (in the presence of anemia) because they promote healing.

Physical and mental rest and relaxation or calm are undoubtedly important therapeutic factors. Bed-rest and sedation, until evidence that the penetrating nature of the crater has disappeared, are decidedly indicated; the same applies to severe distress and manifest hemorrhage. Belladonna or atropine sulfate, by decreasing the volume output of acid, should help to obtain and maintain neutralization, and by this means and by decreasing tonic motility should promote healing and the relief of pain. The administration of these drugs just before retiring is sometimes helpful in controlling night distress. Mineral oil or magnesium carbonate may be used as indicated for constipation.

It is now well established that from 85 to 95 per cent of patients obtain relief within two weeks when hospitalized and placed on s medical management.

A schedule of frequent feedings with or without an antacid and w or without hospitalization will provide relief from distress within two three days in at least 85 per cent of patients. A large portion of the mainder require bed-rest and careful attention to the maintenance complete or partial neutralization of the free acidity.

The crater of a duodenal or gastric ulcer will usually disappear wit 50 days, and sometimes within 10 days, when the patient follows a regim of frequent feedings of a semiliquid or a soft, bland diet of high ac buffering capacity or with one of the antacids. On the other hand, so benign craters disappear very slowly under a very strict regimen. Thou there is no good evidence showing that hospitalization and bed-rest w increase the rate of filling in of the crater, it is well known that most tients who fail to respond to ambulatory management will do so when same treatment is given with rest in bed.

The tendency toward recurrences varies in different patients and t must be taken into consideration in evaluating various therapies. Cert features of the disease, obtained from the history and response to therap have prognostic value in revealing this tendency.

A complete Sippy management prevents recurrences better than oth medical regimens, perhaps because it keeps the patient under care control for a longer period and indoctrinates the patient regarding d and a hygienic mode of life. This regimen, when followed strictly, has recurrence rate of 9 per cent the first year; 19 per cent the second; 30 p cent the third; 40 per cent the fourth; and 45 per cent the fifth. On oth medical therapies, the percentage of patients developing recurrenc ranges from 40 to 80 per cent for the first year, 40 to 85 for the secon 60 to 90 for the third, and 65 to 95 for the fourth and fifth years.

It is generally agreed, though further evidence is required, th approximately 80 per cent of ulcer patients respond satisfactorily medical management over a period of years. Most authors indicate th carelessness on the part of the patient in following a prescribed diet an schedule of rest and vacation and in maintaining a calm attitude of mind is the principal cause of recurrences.

The data available on the use of x-rays to decrease gastric secretio indicate that in a relatively intractable group of patients healing w promoted, and the incidence of recurrences was reduced from an anti ipated rate of 65 per cent to a rate of 32 per cent during a 2.5 year perio These results cannot be safely compared with the results given above f the complete Sippy management, with which they closely agree, becau

ubtably represent results on a more favorable group of patients.
mortality under the medical management of massive hemorrhage
nitely improved in recent years, so that the gross mortality is under
nt and the net mortality is under 1.5 per cent. The improvement
n associated with the prevention of dehydration, the liberal use of
ransfusions, and the feeding of a soft diet as soon as tolerated by
ient. When the internist receives a patient who is not in a state of
ctive shock, the least that can be done therapeutically is to maintain
ient so that he is or remains a fair to good surgical risk.

Surgical Therapy

s widely agreed that surgical therapy is reserved for patients who
ot responded well to medical therapy. The indications for surgery
ays relative and should be considered in relation to each individual
In recent years, the trend has been to operate on fewer patients
use a more radical surgical procedure. The usual indications are
tion, acute, severe, or chronic recurrent hemorrhage, acute per-
n, intractable pain and frequent recurrences, and gastric ulcer
ed of being cancer.

hen surgery is indicated, the major problem is to select a procedure
offers the greatest chance of preventing recurrences, a low mortality,
low postoperative morbidity.

struction, operation is indicated when the degree of retention does
initely decrease on medical management and the general condition
patient does not improve. The operation of choice is based on the
riteria as in the case of elective operations for peptic ulcer without
ction.

acute massive hemorrhage, emergency surgical intervention should be
y considered when the diagnosis of peptic ulcer is certain and
he clinical condition of the patient, the blood pressure, and other
indicate that the bleeding is continuing or when a relapse occurs
ical management in the hospital. In such patients, the mortality on
ed medical management appears to be 50 per cent and on modern
management 10 per cent. The mortality is higher when surgery
rmed later than 48 hours after the onset of continued or relapsing
nage. An operation is usually indicated only when the patient's
n is suitable for a gastric resection.

eciding on an elective operation for chronic recurrent massive hem-
e crucial question is whether a patient who has experienced more
episodes of bleeding is more likely to bleed after surgical manage-
an after continued medical management. The evidence indicates
group of such patients, 66 per cent will bleed again on continued

medical management, 23 per cent after gastroenterostomy, and 11 per cent after gastric resection during a period of from three to five years. Gastric resection, during or after the convalescent period, would appear to be the operation of choice. Since the gross mortality of manifest hemorrhage under medical management is 5 per cent, the gross mortality for elective gastric resection in general should not be much greater, if any. The presence of intractable pain or obstruction in association with hemorrhage increases the indications for surgery. Advancing age increases the mortality of acute and chronic recurrent hemorrhage as well as of gastric resection.

Acute perforated peptic ulcer is generally considered to be a direct and immediate indication for operation. However, acute and subacute perforation, both early and late, have been treated successfully by nonoperative gastric drainage. At present, simple closure carries a mortality rate of about 10 per cent and is the best and safest mode of therapy. However, recurrences occur in 66 per cent of the patients treated with simple closure, and 18 per cent require further surgery. In the hands of skilled and experienced gastric surgeons, gastric resection is safe in early, favorable cases of perforated ulcer and may be indicated in selected cases.

In deciding whether to perform a resection for a gastric ulcer, the chance of 6.5 per cent of carefully diagnosed benign gastric ulcers being malignant and the incident morbidity of a benign gastric ulcer on medical management must be weighed against the 4 or 5 per cent mortality (2 to 3 per cent in some hands) and the 5 to 10 per cent morbidity of a gastric resection.

Intractable pain and frequent recurrences as indications for surgery are the subject of considerable variation in opinion, because they do not constitute a threat to life. The variation in opinion regarding these indications is the chief cause of the variation in the number of peptic ulcer patients submitted to operation by different authors. The extent of the mortality and morbidity consequent to the surgical procedure in relation to that of the continuance of nonoperative management should be the deciding factor.

The surgical mortality of elective simple gastroenterostomy ranges from 1 to 7 per cent, the average being less than 4 per cent. Within the last few years, this has probably been reduced to less than 2 or 3 per cent. In some hands, the surgical mortality for gastric resection is not much larger (4 or 5 per cent), though that for gastric resection for anastomotic ulcer is approximately twice as large (10 per cent). The average surgical mortality of vagotomy is approximately 1.5 per cent.

A summary of the late results of the more widely used operative procedures for the elective surgical therapy of peptic ulcer is shown in Table

209. Among the drainage operations, simple gastroenterostomy is superior to gastroenterostomy with pyloric exclusion and to pyloroplasty. The results following gastric resection appear to be superior to those following

Table 209

SUMMARY OF LATE RESULTS OF OPERATIVE PROCEDURES FOR PEPTIC ULCER*

Procedure	*Satisfactory Results*		*Recurrences*		*Symptom-free Per Cent*	*Worse or No Better Per Cent*
	Average Per Cent of All Cases	*Average and Range of Percentages of All Authors*	*Average Per Cent of All Cases*	*Average and Range of Percentages of All Authors*		
GE for DU†	78	75 (37–98)	9.6	14.5 (2–35)	60	13.5
GE for pyloric ulcer	87	79 (72–93)	..	..	..	..
GE for GU	70	65 (23–83)	18.1	12 (0–44)	57	18.2
GE for peptic ulcer†	73	71 (54–92)	10.3	11.5 (1.1–30)	52	22.7
GE for peptic ulcer‡	..	..	19.4	20.5 (5.6–35)	..	..
GE with exclusion	58	60 (48–68)	23.5	23 (16–36)	..	..
Pyloroplasty	82§	68.2 (37–92)	29.0¶	..	30	29.2
GR for DU	93	92.2 (82–98)	5.1	4.1 (0–11)	46	..
GR for GU	95	95.9 (90–100)	1.1	1.4 (0–7.5)	64	..
GR for peptic ulcer	90	90 (84–96)	2.2	2.5 (0.6–5.0)	70	..
Vagotomy for DU	77‖	69 (64–84)	10.9	..	..	..
Vag + GE or Py. for DU	90	90 (88–100)	3.8	..	..	..
Vag. for PU	87	..	13.5	..	..	..
Medical: complete Sippy	56–90	..	50	..	25	..
Medical: various treatments	50–80	..	73	..	13	..

* Derived from detailed data presented in Chapters 23 and 24.

† Represents all cases, both recent and old.

‡ Represents cases reported since 1939 in which the indications for surgery probably are similar to those for gastric resection today.

§ This figure is probably too high, and is closer to 68 per cent.

¶ An estimate.

‖ Followed for relatively short duration.

Note: The data for medical therapy are from Emery and Monroe (ref. 180, Chapter 22) and Jordan and Kiefer (ref. 182).

gastroenterostomy. After gastric resection, satisfactory results are obtained in approximately 92 per cent of patients, as compared with 75 per cent after gastroenterostomy. After gastric resection, recurrences occur in only approximately 3 per cent of patients, as compared with 11 per cent after

gastroenterostomy. After gastric resection, approximately 60 per cent of patients are symptom-free, as compared with 55 per cent after gastroenterostomy. Though 11 per cent of patients experience postcibal distress after gastric resection, it is severe in only 2.5 per cent. And, though the incidence of postcibal distress and anemia tend to be higher after gastric resection, the incidence of recurrences and severe postcibal distress is so low as to yield a higher percentage of satisfactory results after resection than after gastroenterostomy. At least this appears to be the case on the basis of the evidence now available, which should be additionally weighted in favor of gastric resection because the patients which have been subjected to gastric resection probably represent a more intractable group than those subjected to gastroenterostomy. The incidence of recurrent ulcers following gastroenterostomy is 19.4 per cent, based on reports appearing in the last 10 years.

Vagotomy alone in the hands of the average experienced surgeon appears to yield no better results than simple gastroenterostomy, since the incidence of recurrences and unsatisfactory results is approximately the same, the incidence of recurrences being approximately 12 per cent and the incidence of persistent postcibal distress and diarrhea being approximately 11 per cent. However, when vagotomy is combined with a drainage operation, the incidence of recurrences (3.8 per cent) and of retention and diarrhea (5 per cent) is reduced so that the late results, at present, compare favorably with those of gastric resection. Also, if the existing literature is dependable, it appears that the percentage of symptom-free patients is greater with vagotomy plus a drainage operation than with a gastric resection. Vagotomy appears to be especially applicable to the operative treatment of anastomotic ulcer because it is attended with a mortality of 1.5 per cent, as compared to a mortality of 10 per cent for gastric resection. (It should be realized that these summarizing statements regarding vagotomy may have to be altered in a few years as more late results are reported in the literature.)

A comparison of the results of the medical and surgical management of those ulcer patients who have been hospitalized indicates that surgery promises fewer recurrences and a greater chance of becoming continuously symptom-free. However, the mortality of medical management is lower than that of surgical management. Older statistics (Table 210) indicate that the mortality of medically treated patients who have been hospitalized is approximately 3.4 per cent. This figure is probably too high today, in view of the improved methods of treating hemorrhage and perforation. At the present time, a mortality of less than 2 per cent for medical management over a period of years is more accurate (Table 211, Part I). The mortality figure of either 2 or 3.4 per cent for medical management is

Table 210

MORTALITY RATE OF MEDICALLY TREATED PATIENTS (DEATHS DIRECTLY DUE TO ULCER, EXCLUDING ELECTIVE OPERATIVE PROCEDURES)

Author	Year	Type of Patient	Duration of Follow-up	No. Cases Followed	Deaths (No. and Per Cent)
et al. (1)	1944	Hospitalized	0–10 yr.	651	22 (3.5%)
(2)	1930	Hospitalized	2½–15 yr.	1130	37* (3.3%)
(3)	1945	Hospitalized	5–12 yr.	626	21 (3.4%)

* An additional 45, or 4.0 per cent, died from unknown causes

than the figure of 4 or 5 per cent for the immediate mortality of resection. Since the incidence of anastomotic ulcer is so low after resection (3 per cent), the late mortality (0.4 per cent) (Table 211,) does not add much to the immediate mortality. (It is too early to vagotomy into such a comparison.) Thus, in making the decision en continued medical management and gastric resection in the cent of patients who are difficult to manage medically, the some- higher mortality and decreased morbidity of gastric resection must ighed against the lower mortality and higher morbidity of medical gement.

Table 211

INCIDENCE OF MAJOR CAUSES OF DEATH IN PERSONS DYING OF PEPTIC ULCER

Part I: Deaths Occurring under Medical Management

enty-five of 100 PU patients bleed and 3.5 per cent of the 25, or 0.875, die. ive of 100 PU patients perforate and 10 per cent of the 12, or 1.2, die. al, approximately 2.0 per cent die of hemorrhage and perforation.

Part II: Deaths Occurring under Surgical Management

nty-five of 100 postresection anastomotic ulcers bleed with a mortality of 3.5 per ent, or 1.5 die of hemorrhage.

of 100 postresection anastomotic ulcers perforate with a mortality of 10 per ent (the mortality is probably less than 10 per cent today), or 1.0 die of foration.

of 100 postresection anastomotic ulcers require reoperation with a mortality f 15 per cent, or 9 die from reoperation.

al, the overall mortality of anastomotic ulcer is 1.5 + 1.0 + 9.0 = 11.5. [Since e incidence of anastomotic ulcer after gastric resection is only 3 per cent, the sk of death from one of the complications of resection is only 0.4 per cent.] ation reduces the mortality to 3.0 per cent, according to present data, but the incidence of recurrences after vagotomy is problematic.]

It is indeed fortunate and a credit to the profession that when medical management fails to provide adequate relief in the intractable type of ulcer patient, surgery can provide a greater likelihood of relief with only a relatively small increase in mortality risk.

Everyone, however, looks forward to the day when mutilating operations will be unnecessary. Present knowledge provides the basis for the hope that future research will reveal an orally active, innocuous substance for specifically preventing the formation of acid by the parietal cell and for rendering the gastric and duodenal mucosa less susceptible to injury.

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